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(54) Title: METHODS AND COMPOSITIONS FOR TREATING UROLOGICAL DISORDERS USING 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 OR 6351 MO

(57) Abstract: The present invention relates to methods for the diagnosis and treatment of a urological disorder or urological disorders. Specifically, the present invention identifies the differential expression of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 and 6351 genes in tissues relating to urological disorders, relative to their expression in normal, or non-urological disorders, and/or in response to manipulations relevant to a urological disorder. The present invention describes methods for the diagnostic evaluation and prognosis of various urological disorders, and for the identification of subjects exhibiting a predisposition to such conditions. The invention also provides methods for identifying a compound capable of modulating a urological disorder or urological disorders. The present invention also provides methods for the identification and therapeutic use of compounds as treatments of urological disorders.

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**METHODS AND COMPOSITIONS FOR TREATING UROLOGICAL
DISORDERS USING 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032,
46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 OR 6351
MOLECULES**

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Related Applications

[0001] The present application claims the benefit of U.S. Provisional Application serial No. 60/349, 511, filed on January 18, 2002, of U.S. Provisional Application serial No. 60/360,500, filed on February 28, 2002, of U.S. Provisional Application serial No. 60/365,041, filed on March 15, 2002, of U.S. Provisional Application serial No. 60/374,063, filed on April 19, 2002, of U.S. Provisional Application serial No. 60/403,468, filed on August 14, 2002, of U.S. Provisional Application serial No. 60/414,262, filed on September 27, 2002, of U.S. Provisional Application serial No. 60/419,986, filed on October 21, 2002, of U.S. Provisional Application serial No. 60/423,809, filed on November 5, 2002, and of U.S. Provisional Application serial No. 60/429,797, filed on November 26, 2002. The entire contents of these provisional patent applications are hereby incorporated by this reference.

Background of the Invention

[0002] There are several types of urinary incontinence (UI), the two most common ones being stress urinary incontinence (SUI) and urge urinary incontinence (UUI). SUI can co-exist with UUI and is then referred to as mixed urinary incontinence. UUI is part of a complex known as overactive or oversensitive bladder, which include symptoms of frequency and/or urgency with or without UUI. 75% of patients with incontinence are elderly females.

[0003] Bladder overactivity may result from detrusor instability or hyperreflexia. Triggers may include increased activity of afferent peripheral nerve terminals in the bladder or decreased inhibitory control in the central nervous system and/or in peripheral ganglia. Changes in detrusor muscle structure or function, such as increased muscle cell excitability due to denervation, may also play a role in the pathogenesis of this filling disorder.

[0004] Benign prostatic hyperplasia (BPH) is a common age-related pathological condition that affects men worldwide. At 60 years of age, at least 25% have symptoms of BPH. The symptoms of BPH are currently referred to as lower urinary tract symptoms (LUTS). LUTS are traditionally divided into obstructive (weak stream, intermittency,

straining, etc.) and irritative (frequency, nocturia, urgency, etc.) symptoms. They are caused by at least three pathophysiological components, *i.e.*, static, dynamic and bladder detrusor-related. Prostate enlargement, or more specifically benign prostatic nodular enlargement, accounts for much of the static obstructive element and in the elderly male is
5 mainly confined to the transition zone and periurethral glandular tissue. By contrast the dynamic component is a reflection of smooth muscle tone in the prostate and the bladder neck. Variations in muscle tone cause corresponding changes in the degree of outlet obstruction. Bladder and detrusor-related components are believed to predominate in those with principally irritative symptoms. They reflect an increase in the incidence of
10 uninhibited detrusor contractions and at the same time a loss of contractile ability of the bladder, both of which are a response to existing obstruction.

[0005] There is an unmet medical need for therapeutics useful for UI and BPH.

Detailed Description of the Invention

[0006] The present invention provides methods and compositions for the diagnosis
15 and treatment of urological disorders, including but not limited to UI and BPH. Urological disorders as used herein can be diseases of the bladder including but not limited to urinary incontinence including overactive/oversensitive bladder, overflow urinary incontinence, stress urinary incontinence caused by dysfunction of the bladder, urethra or central/peripheral nervous system.

20 [0007] As used herein a urological disorder can be a disorder of the prostate including but not limited to "a prostate disorder" which refers to an abnormal condition occurring in the male pelvic region characterized by, e.g., male sexual dysfunction and/or urinary symptoms. This disorder may be manifested in the form of genitourinary inflammation (e.g., inflammation of smooth muscle cells) as in several common diseases of
25 the prostate including prostatitis, benign prostatic hyperplasia and cancer, e.g., adenocarcinoma or carcinoma, of the prostate.

[0008] As used herein a urological disorder can be a disorder of the kidney including but not limited to congenital anomalies including, but not limited to, cystic diseases of the kidney, that include but are not limited to, cystic renal dysplasia, autosomal dominant
30 (adult) polycystic kidney disease, autosomal recessive (childhood) polycystic kidney disease, and cystic diseases of renal medulla, which include, but are not limited to, medullary sponge kidney, and nephronophthisis-uremic medullary cystic disease complex, acquired (dialysis-associated) cystic disease, such as simple cysts; glomerular diseases including pathologies of

glomerular injury that include, but are not limited to, in situ immune complex deposition, that includes, but is not limited to, anti-GBM nephritis, Heymann nephritis, and antibodies against planted antigens, circulating immune complex nephritis, antibodies to glomerular cells, cell-mediated immunity in glomerulonephritis, activation of alternative complement pathway,

5 epithelial cell injury, and pathologies involving mediators of glomerular injury including cellular and soluble mediators, acute glomerulonephritis, such as acute proliferative (poststreptococcal, postinfectious) glomerulonephritis, including but not limited to, poststreptococcal glomerulonephritis and nonstreptococcal acute glomerulonephritis, rapidly progressive (crescentic) glomerulonephritis, nephrotic syndrome, membranous

10 glomerulonephritis (membranous nephropathy), minimal change disease (lipoid nephrosis), focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, IgA nephropathy (Berger disease), focal proliferative and necrotizing glomerulonephritis (focal glomerulonephritis), hereditary nephritis, including but not limited to, Alport syndrome and thin membrane disease (benign familial hematuria), chronic glomerulonephritis, glomerular

15 lesions associated with systemic disease, including but not limited to, systemic lupus erythematosus, Henoch-Schönlein purpura, bacterial endocarditis, diabetic glomerulosclerosis, amyloidosis, fibrillary and immunotactoid glomerulonephritis, and other systemic disorders; diseases affecting tubules and interstitium, including acute tubular necrosis and tubulointerstitial nephritis, including but not limited to, pyelonephritis and urinary tract

20 infection, acute pyelonephritis, chronic pyelonephritis and reflux nephropathy, and tubulointerstitial nephritis induced by drugs and toxins, including but not limited to, acute drug-induced interstitial nephritis, analgesic abuse nephropathy, nephropathy associated with nonsteroidal anti-inflammatory drugs, and other tubulointerstitial diseases including, but not limited to, urate nephropathy, hypercalcemia and nephrocalcinosis, and multiple myeloma;

25 diseases of blood vessels including benign nephrosclerosis, malignant hypertension and accelerated nephrosclerosis, renal artery stenosis, and thrombotic microangiopathies including, but not limited to, classic (childhood) hemolytic-uremic syndrome, adult hemolytic-uremic syndrome/thrombotic thrombocytopenic purpura, idiopathic HUS/TTP, and other vascular disorders including, but not limited to, atherosclerotic ischemic renal disease,

30 atheroembolic renal disease, sickle cell disease nephropathy, diffuse cortical necrosis, and renal infarcts; urinary tract obstruction (obstructive uropathy); urolithiasis (renal calculi, stones); and tumors of the kidney including, but not limited to, benign tumors, such as renal papillary adenoma, renal fibroma or hamartoma (renomedullary interstitial cell tumor), angiomyolipoma, and oncocytoma, and malignant tumors, including renal cell carcinoma

(hypernephroma, adenocarcinoma of kidney), which includes urothelial carcinomas of renal pelvis.

[0009] "Treatment", as used herein, is defined as the application or administration of a therapeutic agent to a patient, or application or administration of a therapeutic agent to an isolated tissue or cell line from a patient, who has a disease or disorder, a symptom of disease or disorder or a predisposition toward a disease or disorder, with the purpose of curing, healing, alleviating, relieving, altering, remedying, ameliorating, improving or affecting the disease or disorder, at least one symptom of disease or disorder or the predisposition toward a disease or disorder. A therapeutic agent includes, but is not limited to, small molecules, peptides, antibodies, ribozymes and antisense oligonucleotides. Representative molecules are described herein.

[0010] The present invention is based, at least in part, on the discovery that nucleic acid and protein molecules, (described infra), are differentially expressed in disease states relative to their expression in normal, or non- disease states. The modulators of the molecules of the present invention, identified according to the methods of the invention can be used to modulate (*e.g.*, inhibit, treat, or prevent) or diagnose a disease, including, but not limited to, UI and BPH.

[0011] "Differential expression", as used herein, includes both quantitative as well as qualitative differences in the temporal and/or tissue expression pattern of a gene. Thus, a differentially expressed gene may have its expression activated or inactivated in normal versus disease conditions. The degree to which expression differs in normal versus disease or control versus experimental states need only be large enough to be visualized via standard characterization techniques, *e.g.*, quantitative PCR, Northern analysis, subtractive hybridization. The expression pattern of a differentially expressed gene may be used as part of a prognostic or diagnostic a disease, *e.g.*, UI and BPH, evaluation, or may be used in methods for identifying compounds useful for the treatment of a disease, *e.g.*, UI or BPH. In addition, a differentially expressed gene involved in a disease may represent a target gene such that modulation of the level of target gene expression or of target gene product activity will act to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve or affect a disease condition, *e.g.*, UI and/or BPH. Compounds that modulate target gene expression or activity of the target gene product can be used in the treatment of a disease. Although the genes described herein may be differentially expressed with respect to a disease, and/or their products may interact with gene products important to a disease, the genes may also be involved in mechanisms important to additional disease cell processes.

Molecules of the Present Invention

- 5 [0012] The molecules of the present invention include but are not limited to the following classifications: G protein coupled receptors (GPCRs). GPCRs of lipid mediators and ligand-gated ion channels have been implicated in increased afferent nerve activity, especially in c-fibers. Enzymes catabolizing/ metabolizing neurotransmitters, neurotransmitter/peptide hormone GPCRs, proteases/ peptidases and transporters have been shown to participate in a) decreased inhibitory control in CNS/peripheral ganglia, b) increased excitatory neurotransmission in CNS/peripheral ganglia, and c) increased sensitivity to efferent stimulation in the detrusor. Enzymes catabolizing/metabolizing cAMP/cGMP, ligand-gated ion channels, $\text{Ca}^{2+}/\text{K}^{+}$ channels, Ser/Thr-kinases and ATPases have been implicated in myogenic regulation of bladder smooth muscle contraction. Involvement of neurotransmitter GPCRs and enzymes catabolizing/metabolizing cAMP/cGMP has been demonstrated in neurological and myogenic regulation of the storage reflex of the bladder.
- 15 [0013] Peptide hormone GPCRs, proteinases/peptidases, enzymes catabolizing/metabolizing steroids and nuclear hormone receptors have been shown to be involved in the endocrine regulation of testosterone production. Receptor tyrosine kinases and Ser/Thr-kinases have been implicated in mediating the initial epithelial growth in BPH through stromal cell-derived growth factors and local factors. Peptide hormone/neurotransmitter GPCRs and transporters have been demonstrated to mediate the neurological regulation of the smooth muscle tone. Enzymes catabolizing/metabolizing cAMP/cGMP, ligand-gated ion channels, $\text{Ca}^{2+}/\text{K}^{+}$ channels, ATPases have been implicated in myogenic regulation of smooth muscle tone in the prostate.
- 20

25 **Gene ID 1435**

- [0014] The human 1435 sequence (SEQ ID NO:1), (GI:183931, known also as human receptor tyrosine kinase, eph-A3) which is approximately 3149 nucleotides long including untranslated regions, contains a predicted methionine-initiated coding sequence of about 2952 nucleotides, including the termination codon (nucleotides indicated as coding of SEQ ID NO:1, SEQ ID NO:3). The coding sequence, located at about nucleic acids 101 to 3052 of SEQ ID NO:1, encodes a 983 amino acid protein (SEQ ID NO:2) (GI:183932).
- 30

[0015] As assessed by TaqMan analysis, 1435 mRNA showed very restricted expression in normal tissues limited to prostate, including benign prostatic hyperplasia

(BPH) and brain. TaqMan analysis revealed that 1435 mRNA was up-regulated in 4 different BPH samples compared to 3 normal prostate samples. Additional TaqMan studies showed that 1435 mRNA was mainly localized to the stromal component although there was some expression in the epithelium of the prostate. 1435 is a tyrosine kinase receptor.

5 Tyrosine kinase receptors play central roles in the growth and differentiation of normal and tumor cells. Most proteins found to interact with receptors are well-known regulators of cytoskeletal organization and cell adhesion. In response to ephrin-A (a ligand for 1435), a new guanine nucleotide exchange factor for the Rho-family of GTPases, ephexin, activates RhoA that in turn activated Rho kinases. Rho kinase activation inhibits myosin light chain
10 phosphatase that leads to an increase in myosin activity and promotes contractility of the actinomyosin network. Antagonizing 1435 (eph-A3) will block activation of rho kinase and thus block the contractil property of the stromal component in BPH. Agents which antagonize 1435 activity would inhibit prostatic hyperplasia and be useful as therapeutics for BPH.

15

Gene ID 559

[0016] The human 559 sequence (SEQ ID NO:4), (GI:31657, known also as GAT1 GABA transporter) which is approximately 2298 nucleotides long including untranslated regions, contains a predicted methionine-initiated coding sequence of about 1800
20 nucleotides, including the termination codon (nucleotides indicated as coding of SEQ ID NO:4, SEQ ID NO:6). The coding sequence, located at about nucleic acids 235 to 2034 of SEQ ID NO:4, encodes a 599 amino acid protein (SEQ ID NO:5) (GI:31658).

[0017] As assessed by TaqMan analysis, 559 mRNA was upregulated in 4/4 BPH prostates as compared to 2 normal prostates by a factor of 4-25 fold. Additional TaqMan
25 analyses on normal human tissues show a high level of 559 mRNA expression in neuronal tissue and liver.

[0018] 559 is the GABA transporter GAT-1. GABA action at the GABA A receptor results in hyperpolarization of synapses by Cl-ion influx). The GABA transporter pumps GABA from outside into the cell. Blocking the GABA transporter would lead to an
30 increased amount of GABA at the synapse/muscular-neuronal connection, which would result in hyperpolarization and, thus, in an inhibitory effect on smooth muscle cell contraction. Due to its functional role and its expression pattern, modulators of 559 activity would be useful in treating urological disorders, including but not limited to BPH.

559 polypeptides of the present invention are useful in screening for modulators of 559 activity.

Gene ID 34021

5 [0019] The human 34021 sequence (SEQ ID NO:7), which is approximately 1559 nucleotides long including untranslated regions, contains a predicted methionine-initiated coding sequence of about 1104 nucleotides, including the termination codon (nucleotides indicated as coding of SEQ ID NO:7, SEQ ID NO:9). The coding sequence, located at about nucleic acids 85 to 1188 of SEQ ID NO:7, encodes a 367 amino acid protein (SEQ
10 ID NO:8).

[0020] 34021 is a protein kinase, called TSK-1. As assessed by TaqMan analysis, 34021 mRNA was expressed at low to moderate levels with highest expression levels in benign prostatic hyperplasia (BPH) and prostate tumor samples. Additional TaqMan analyses indicate that 34021 mRNA was upregulated in a majority of BPH prostates vs
15 normal prostates. Due to its expression pattern, modulators of 34021 activity would be useful in treating urological disorders including but not limited to BPH and urinary incontinence. 34021 polypeptides of the current invention would be useful in screening for modulators of 34021 activity.

Gene ID 44099

[0021] The human 44099 sequence (SEQ ID NO:10), which is approximately 1389 nucleotides long including untranslated regions, contains a predicted methionine-initiated coding sequence of about 1380 nucleotides, including the termination codon (nucleotides indicated as coding of SEQ ID NO:10, SEQ ID NO:12). The coding sequence, located at
25 about nucleic acids 1 to 1380 of SEQ ID NO:10, encodes a 459 amino acid protein (SEQ ID NO:11).

[0022] 44099 is an ion channel known as the P2X2 receptor. As assessed by TaqMan analysis showed low to moderate 44099 mRNA expression in the normal prostate and upregulated elevated in the majority of BPH samples. Additional TaqMan analyses
30 showed that 44099 mRNA was upregular in 5/5 BPH samples compared to normal prostates and that 44099 is expressed in the stromal component of the prostate BPH.

[0023] P2X receptors are ligand gated ion channels (ligand in this case: ATP). They are known to mediate synaptic transmission between neurons and from neurons to smooth muscle. Due to its function and expression pattern, modulating the activity of 44099 would

modulate smooth muscle tone in the BPH prostate. Modulators of 44099 activity would be useful in treating urological disorders including but not limited to BPH. 44099 polypeptides of the current invention would be useful in screening for modulators of 44099 activity.

5

Gene ID 25278

[0024] The human 25278 sequence (SEQ ID NO:13), which is approximately 2940 nucleotides long including untranslated regions, contains a predicted methionine-initiated coding sequence of about 1710 nucleotides, including the termination codon (nucleotides indicated as coding of SEQ ID NO:13, SEQ ID NO:15). The coding sequence, located at about nucleic acids 334 to 2043 of SEQ ID NO:13, encodes a 569 amino acid protein (SEQ ID NO:14).

[0025] As assessed by TaqMan analysis, 25278 mRNA was upregulated in a rat model for UI, the spinal cord injury (SCI) model. Additional TaqMan studies showed that 25278 mRNA was upregulated in all BPH samples vs normal prostate. Due to its expression pattern, modulators of 25278 activity would be useful in treating urological disorders, including but not limited to BPH and UI. 25278 polypeptides of the current invention would be useful in screening for modulators of 25278 activity.

20 **Gene ID 641**

[0026] The human 641 sequence (SEQ ID NO:16), also known as a potassium channel (KCNQ2) which is approximately 3232 nucleotides long including untranslated regions, contains a predicted methionine-initiated coding sequence of about 2619 nucleotides, including the termination codon (nucleotides indicated as coding of SEQ ID NO:16, SEQ ID NO:18). The coding sequence, located at about nucleic acids 128 to 2746 of SEQ ID NO:16, encodes a 872 amino acid protein (SEQ ID NO:17).

[0027] As assessed by TaqMan analysis, 641 mRNA was significantly upregulated in the BPH prostate when compared to expression levels in normal prostate tissues. 641 is a potassium channel known as KCNQ2. Published literature indicates that the activation of 641 or KCNQ2 stabilized the membrane potential of cells by pumping out potassium to hyperpolarize the cells. Therefore, by activating potassium channels, prostate smooth muscles would be hyperpolarized leading to the relaxation of these muscles. The hyperpolarization of prostate smooth muscles will be beneficial to reduce prostatic obstruction of BPH patients. Due to the expression of 641 in BPH, modulators of 641

activity would be useful in treating urological disorders including but not limited to BPH and urinary incontinence. 641 polypeptides of the current invention would be useful in screening for modulators of 641 activity.

5 **Gene ID 260**

[0028] The human 260 sequence (SEQ ID NO:19), also known as a Kappa Opioid Receptor 1 (KOR), is approximately 1182 nucleotides long including untranslated regions, contains a predicted methionine-initiated coding sequence of about 1143 nucleotides, including the termination codon (nucleotides indicated as coding of SEQ ID NO:19, SEQ
10 ID NO:21). The coding sequence, located at about nucleic acids 14 to 1156 of SEQ ID NO:19, encodes a 380 amino acid protein (SEQ ID NO:20).

[0029] As assessed by TaqMan analysis, 260 mRNA was significantly upregulated in human brain tissue, namely the cortex and hypothalamus, along with the dorsal root ganglion (DRG) and lung tissues. Further Taqman analysis indicated that 260 mRNA was
15 expressed in normal prostate and all BPH samples. 260 mRNA was also expressed in the epithelium and stroma cells of the prostate.

[0030] 260 or kappa opioid receptors (KORs) are a member of the opioid family of receptors. The Fas/FasL apoptotic pathway is involved in kappa-opioid-induced apoptosis of human endometrial stromal cells. (Mol Hum Reprod. 2001 Sep;7 (9):867-74). Kappa-
20 Opioid receptors potentiates apoptosis via a phospholipase C pathway in the CNE2 human epithelial tumor cell line (Biochim Biophys Acta. 2000 Dec 11;1499 (1-2):49-62). Agonist activation of kappa opioid receptors are implicated in smooth muscle cell relaxation. In addition, kappa opioid receptors play a significant role in apoptosis of stromal and epithelial cells. Therefore, activation of 260 with agonists results either in smooth muscle
25 relaxation or stromal, epithelial cell apoptosis or both and would be useful in reducing the symptoms of BPH. Due to the expression of 260 in brain cortex, brain hypothalamus and dorsal root ganglion (DRG) and lung tissues, modulators of 260 activity would be useful in treating urological disorders including but not limited to BPH and urinary incontinence. 260 polypeptides of the current invention would be useful in screening for modulators of
30 260 activity.

Gene ID 55089

[0031] The human 55089 sequence (SEQ ID NO: 22), also known as a soluble phospholipase A2, is approximately 2270 nucleotides long including untranslated regions,

contains a predicted methionine-initiated coding sequence of about 636 nucleotides, including the termination codon (nucleotides indicated as coding of SEQ ID NO:22, SEQ ID NO:24). The coding sequence, located at about nucleic acids 93 to 728 of SEQ ID NO:22, encodes a 211 amino acid protein (SEQ ID NO: 23).

5 [0032] As assessed by TaqMan analysis, 55089 mRNA was significantly upregulated in the tonsil followed by colon, bladder and kidney tissues. Further Taqman analysis showed that 55089 mRNA was expressed in bladders at a higher level than heart, liver, kidney or the brain. As assessed by In Situ Hybridization (ISH) experiments performed with a human probe, 55089 was shown to be expressed in human, monkey, 10 rabbit and rat bladder, both in smooth muscle cells and epithelial cells. The expression of 55089 in bladders is relatively higher in epithelial cell compared to smooth muscle cells. 55089 also shows expression in monkey and rat DRG by ISH.

[0033] 55089 is a member of a family of soluble phospholipase A2. In general, phospholipase A2 degrades phospholipids in lipid bilayers by releasing fatty acid in the C2 15 position usually occupied by unsaturated fatty acid like arachidonate in higher organisms. Most of the soluble phospholipase A2 possess two biological functions. One is bactericidal activity by disturbing the integrity of bacterial lipid bilayers, while the other is to supply arachidonate a source of bioactive lipids like prostaglandins and leukotrienes. Unlike the other members, 55089 has no bacterial activity against both gram+ and gram- in in vitro 20 experiment. This result implies that the major role of 55089 is to control arachidonate release. In addition, exogenous leukotrienes and prostaglandins are reported to stimulate bladder contraction in organ bath experiments. Because 55089 plays a role in releasing arachidonate in bladder, inhibiting 55089 potentially modulates bladder smooth muscle tone and is useful in controlling overactive bladder. Due to the expression of 55089 in the 25 tonsil, by colon, bladder and kidney, modulators of 55089 activity would be useful in treating urological disorders including but not limited to BPH and urinary incontinence. 55089 polypeptides of the current invention would be useful in screening for modulators of 55089 activity.

30 **Gene ID 21407**

[0034] The human 21407 sequence (SEQ ID NO:25), also known as CNG channel alpha 3 potassium channel (KCNQ2) which is approximately 3486 nucleotides long including untranslated regions, contains a predicted methionine-initiated coding sequence of about 2085 nucleotides, including the termination codon (nucleotides indicated as

coding of SEQ ID NO:25, SEQ ID NO:27). The coding sequence, located at about nucleic acids 40 to 2124 of SEQ ID NO:25, encodes a 694 amino acid protein (SEQ ID NO:26).

[0035] As assessed by TaqMan analysis, 21407 mRNA was expressed in the pituitary gland followed by brain cortex, brain hypothalamus, spinal cord, bladder, small intestine and colon. Further Taqman analysis indicated that 21407 mRNA was expressed in 7 bladders out of 9 bladders. As assessed by In Situ Hybridization (ISH), experiments performed with a human probe showed expression of 21407 in human and rabbit bladder. Overall, positive epithelial signal was seen in human bladder samples and rabbit bladder samples.

10 [0036] 21407 or CGN3 is a member of the cyclic nucleotide-gated (CNG) cation channels family. CNG3 is one of the alpha subunit and forms functional ion channel with or without the beta subunit. The CNG channels close when there is reduction in cGMP leading to decrease in Ca^{2+} influx and hyperpolarization. The role of CNG channels in phototransduction has been well established. CNG3 has been shown to play significant role
15 in cone function of photoreception. Therefore, inhibiting 21407 with antagonists potentially leads to reduction in Ca^{2+} influx and hyperpolarization, both leading to relaxation or reduction in tone of bladder smooth muscle and may be useful to control overactive bladder. Due to the expression of 21407 in the pituitary gland, brain cortex, brain hypothalamus, spinal cord, bladder, small intestine and colon, modulators of 21407
20 activity would be useful in treating urological disorders including but not limited to BPH and urinary incontinence. 21407 polypeptides of the current invention would be useful in screening for modulators of 21407 activity.

Gene ID 42032

25 [0037] The human 42032 sequence, known also as a calcium activated chloride channel, (SEQ ID NO:28), is approximately 2970 nucleotides long including untranslated regions, contains a predicted methionine-initiated coding sequence of about 2832 nucleotides, including the termination codon (nucleotides indicated as coding of SEQ ID NO:28, SEQ ID NO:30). The coding sequence, located at about nucleic acids 109 to 2940
30 of SEQ ID NO:28, encodes a 943 amino acid protein (SEQ ID NO:29).

[0038] As assessed by TaqMan analysis, 42032 mRNA showed high level of expression in lung tumors followed by brain cortex, normal bladder, BPH, prostate tumor, normal breast and normal tonsil. Further Taqman analysis showed that 42032 mRNA was expressed in 7/9 bladders and normal and BPH prostate.

[0039] 42032 (CLCA2/CaCC3) belongs to a class of calcium activated chloride (CLCA) channels. CLCA channels contribute to the membrane potential. The CLCA channels are activated by calcium and cause membrane depolarization leading to increase Ca^{2+} influx eventually increasing smooth muscle tone. Blocking the CLCA channels can lead to hyperpolarization and smooth muscle relaxation. Therefore, blocking 42032 with antagonists can cause membrane hyperpolarization which in turn reduces Ca^{2+} influx leading to relaxation or reduction of bladder smooth muscle tone and is potentially useful in controlling overactive bladder. Due to 42032 expression in lung tumors, brain cortex, normal bladder, BPH, prostate tumor, normal breast and normal tonsil, modulators of 42032 activity would be useful in treating urological disorders including but not limited to BPH and urinary incontinence. 42032 polypeptides of the current invention would be useful in screening for modulators of 42032 activity.

Gene ID 46656

[0040] The human 46656 sequence known also as a calcium activated chloride channel (SEQ ID NO:31), is approximately 3204 nucleotides long including untranslated regions, contains a predicted methionine-initiated coding sequence of about 2754 nucleotides, including the termination codon (nucleotides indicated as coding of SEQ ID NO:31, SEQ ID NO:33). The coding sequence, located at about nucleic acids 29 to 2782 of SEQ ID NO:31, encodes a 917 amino acid protein (SEQ ID NO:32).

[0041] As assessed by TaqMan analysis, 46656 mRNA was expressed at high levels in colon tissues followed by brain cortex, lung tumor and bladder tissues. Further TaqMan analysis showed 46656 expression in 8/9 bladders and normal and BPH prostate.

[0042] 46656 (CLCA4/CaCC2) belongs to a class of calcium activated chloride (CLCA) channels. CLCA channels contribute to the membrane potential. The CLCA channels are activated by calcium and cause membrane depolarization leading to increase Ca^{2+} influx eventually increasing smooth muscle tone. Blocking the CLCA channels can lead to hyperpolarization and smooth muscle relaxation. Therefore, the blocking of 46656 with antagonists can cause membrane hyperpolarization which in turn reduces Ca^{2+} influx leading to relaxation or reduction of bladder smooth muscle tone and is potentially useful in controlling overactive bladder. Due to 46656 expression the colon, brain cortex, lung tumor and bladder tissues and its functional role, modulating the activity of 46656 would modulate smooth muscle tone in the BPH prostate. Modulators of 46656 activity would be useful in treating urological disorders including but not limited to BPH and urinary

incontinence. 46656 polypeptides of the current invention would be useful in screening for modulators of 46656 activity.

Gene ID 62533

5 [0043] The human 62533 sequence, also known as a GPCR, (SEQ ID NO:34), is approximately 1170 nucleotides long including untranslated regions, contains a predicted methionine-initiated coding sequence of about 1170 nucleotides, including the termination codon (nucleotides indicated as coding of SEQ ID NO:34, SEQ ID NO:36). The coding sequence, located at about nucleic acids 1 to 1170 of SEQ ID NO:34, encodes a 389 amino
10 acid protein (SEQ ID NO:35).

[0044] As assessed by TaqMan analysis, 62553 mRNA was expressed in the testes, dorsal root ganglion (DRG), brain and spinal cord. Rat and mouse TaqMan panels showed that 63553 mRNA was expressed at highest levels in the DRG. As assessed by In Situ Hybridization (ISH) experiments performed with a human probe showed expression in
15 monkey and rat brain, spinal cord and DRG. In the brain, 62553 is mainly expressed in the cortex and in a thalamic nucleus. In the spinal cord 62553 is expressed in the most superficial laminae and around central canal where Aδ- and C-fibers from DRG terminate and also in motor neurons. In monkey and rat DRGs expression is observed in a very restricted subpopulation of small diameter neurons.

20 [0045] Based on the exquisite and restricted expression of 62553 in the peripheral pathways, including sensory neurons in the DRG and their targets within the spinal cord, modulating the activity of 62553 can alter urinary bladder hyperreflexia and can be used for urinary incontinence. Modulators of 62533 activity would be useful in treating urological disorders, including but not limited to BPH and urinary incontinence. 62533
25 polypeptides of the current invention would be useful in screening for modulators of 62533 activity.

Gene ID 302

[0046] The human 302 sequence (SEQ ID NO:37) is approximately 1159
30 nucleotides long including untranslated regions, contains a predicted methionine-initiated coding sequence of about 1074 nucleotides, including the termination codon (nucleotides indicated as coding of SEQ ID NO:37, SEQ ID NO:39). The coding sequence, located at about nucleic acids 64 to 1137 of SEQ ID NO:37, encodes a 357 amino acid protein (SEQ ID NO:38).

[0047] 302 is a GPCR known as 5-hydroxytryptamine 5A (5-HT-5A) (Serotonin receptor). As assessed by TaqMan analysis, 302 mRNA showed high levels of expression in brain followed by dorsal root ganglion (DRG) and spinal cord. Additional TaqMan analysis showed that 302 mRNA was upregulated in the DRG in rat models for UI, the
5 spinal cord injury (SCI), and in aged and bladder outlet obstruction (BOO) models.

[0048] Serotonin receptors have been implicated in regulating smooth muscle contraction/relaxation. Due to its function and expression pattern, modulating the activity of 302 would modulate urinary bladder reflex and/or hyperreflexia. Modulators of 302 activity would be useful in treating urological disorders including but not limited to urinary
10 incontinence. 302 polypeptides of the current invention would be useful in screening for modulators of 302 activity.

Gene ID 323

[0049] The human 323 sequence (SEQ ID NO:40) is approximately 1984
15 nucleotides long including untranslated regions, contains a predicted methionine-initiated coding sequence of about 1323 nucleotides, including the termination codon (nucleotides indicated as coding of SEQ ID NO:40, SEQ ID NO:42). The coding sequence, located at about nucleic acids 468 to 1790 of SEQ ID NO:40, encodes a 440 amino acid protein (SEQ ID NO:41).

[0050] 323 is a GPCR called 5-hydroxytryptamine 6 receptor (5-HT-6) (Serotonin receptor). As assessed by TaqMan analysis, 323 mRNA was expressed at low levels with the highest levels in brain, skin and normal prostate. Additional TaqMan analyses showed that 323 mRNA is upregulated in 10/11 BPH samples, including peripheral and transitional zone samples, as compared to normal prostate samples. A rat TaqMan panel showed
25 upregulation of 323 in rat bladder and in a spinal cord injured (SCI) rat model. Due to its function and expression pattern, modulating the activity of 323 would modulate smooth muscle tone in the BPH prostate. Modulators of 323 activity would be useful in treating urological disorders including but not limited to BPH. 323 polypeptides of the current invention would be useful in screening for modulators of 323 activity.

30

Gene ID 12303

[0051] The human 12303 sequence (SEQ ID NO:43) is approximately 2772 nucleotides long including untranslated regions, contains a predicted methionine-initiated coding sequence of about 1260 nucleotides, including the termination codon (nucleotides

indicated as coding of SEQ ID NO:43, SEQ ID NO:45). The coding sequence, located at about nucleic acids 64 to 1323 of SEQ ID NO:43, encodes a 419 amino acid protein (SEQ ID NO:44).

5 [0052] 12303 is a potassium channel known as KCNK4 (or TRAAK). As assessed by TaqMan analysis, 12303 mRNA was highly expressed in brain followed by DRG and spinal cord.

[0053] KCNK channels contribute to the membrane potential. Activation of the channels leads to membrane hyperpolarization affecting the frequency and pattern of neuronal firing. Modulators of 12303 activity would cause neuronal membrane
10 hyperpolarization, altering urinary bladder hyperreflexia. Modulators of 12303 would be useful in treating urological disorders, including but not limited to UI. 12303 polypeptides of the current invention would be useful in screening for modulators of 12303 activity.

Gene ID 985

15 [0054] The human 985 sequence (SEQ ID NO:46), known as Neuroendocrine convertase 2, is approximately 2223 nucleotides long including untranslated regions, contains a predicted methionine-initiated coding sequence of about 1917 nucleotides, including the termination codon (nucleotides indicated as coding of SEQ ID NO:46, SEQ ID NO:48). The coding sequence, located at about nucleic acids 88 to 2004 of SEQ ID
20 NO:46, encodes a 638 amino acid protein (SEQ ID NO:47).

[0055] As assessed by TaqMan analysis, 985 mRNA was expressed at high levels in human brain followed by dorsal root ganglion (DRG) and pancreas. 985 mRNA was also expressed in rat brain, spinal cord and DRG. Additional TaqMan analyses indicate that 985 mRNA was upregulated in DRG in a rat model for spinal cord injury (SCI).

25 [0056] Neuroendocrine convertase 2 precursor (NEC2) is also known as prohormone convertase 2 (PC2) or Propotien convertase 2. PC2 is involved in the processing of prodynorphin precursor for generation of dynorphin. Dynorphin is known to inhibit the neuronal activity in DRG by altering ionic current. Due to its function and expression pattern, modulators of 985 activity would modulate production of dynorphin
30 and thus alter the activity of neuronal pathways involved in urinary bladder function, bladder reflex and/or hyperreflexia. Modulators of 985 would be useful in treating urological disorders including but not limited to urinary incontinence. 985 polypeptides of the current invention would be useful in screening for modulators of 985 activity.

Gene ID 13237

[0057] The human 13237 sequence (SEQ ID NO:49), which is approximately 3637 nucleotides long including untranslated regions, contains a predicted methionine-initiated coding sequence of about 3201 nucleotides, including the termination codon (nucleotides indicated as coding of SEQ ID NO:49, SEQ ID NO:51). The coding sequence, located at about nucleic acids 77 to 3277 of SEQ ID NO:49, encodes a 1066 amino acid protein (SEQ ID NO:50).

[0058] 13237 is a protein kinase known as the RSK-like protein kinase. As assessed by TaqMan analysis, 13237 mRNA was expressed at high levels in brain followed by DRG and prostate. Additional TaqMan analyses showed that 13237 mRNA was upregulated in all BPH samples, including peripheral and transitional zone samples, as compared to normal prostates.

[0059] RSKs are known to be activated by ERK and mediate intracellular signals. RSKs phosphorylate cytosolic proteins that are involved in cell proliferation. RSKs are also known to activate Na⁺/H⁺ exchanger (NHE). NHEs play a role in regulating smooth muscle tone. Due to its function and expression pattern, modulating the activity of 13237 would modulate either stromal or epithelial cell apoptosis, or modulate smooth muscle tone in BPH prostate. Modulators of 13237 activity would be useful in treating urological disorders including but not limited to BPH. 13237 polypeptides of the current invention would be useful in screening for modulators of 13237 activity.

Gene ID 13601

[0060] The human 13601 sequence (SEQ ID NO:52), which is approximately 1557 nucleotides long including untranslated regions, contains a predicted methionine-initiated coding sequence of about 1290 nucleotides, including the termination codon (nucleotides indicated as coding of SEQ ID NO:52, SEQ ID NO:54). The coding sequence, located at about nucleic acids 1 to 1290 of SEQ ID NO:52, encodes a 429 amino acid protein (SEQ ID NO:53).

[0061] 13601 is a transporter known as zinc transporter 4. As assessed by TaqMan analysis, 13601 mRNA was expressed at low levels with highest expression levels in BPH and prostate tumor samples, followed by brain, urge urinary incontinence (UUI) bladder and DRG. Additional TaqMan studies showed that 13601 mRNA was upregulated in 8/11 BPH samples, including peripheral and transitional zone samples, as compared to normal prostate.

[0062] Zinc transporters are involved maintaining cellular zinc homeostasis. High levels of cytoplasmic zinc are known to cause cell apoptosis. Accumulation of high levels of intracellular zinc was implicated in the apoptosis of prostate cells by acting on mitochondria and causing the release of cytochrome C. Due to its function and expression pattern, modulators of 13601 activity would modulate zinc concentration in the cytoplasm and lead to cellular apoptosis in BPH prostate. Modulators of 13601 would be useful in treating urological disorders, including but not limited to BPH. 13601 polypeptides of the current invention would be useful in screening for modulators of 13601 activity.

10 **Gene ID 18926**

[0063] The human 18926 sequence (SEQ ID NO:55), which is approximately 1746 nucleotides long including untranslated regions, contains a predicted methionine-initiated coding sequence of about 1596 nucleotides, including the termination codon (nucleotides indicated as coding of SEQ ID NO:55, SEQ ID NO:57). The coding sequence, located at about nucleic acids 28 to 1623 of SEQ ID NO:55, encodes a 531 amino acid protein (SEQ ID NO:56).

[0064] As assessed by TaqMan analysis, 18926 mRNA was expressed at high levels in human brain followed by DRG, spinal cord, pituitary gland and bladder. Expression in rat was restricted to DRG. Additional TaqMan studies showed that 18926 mRNA was upregulated in DRG in a rat model for SCI.

[0065] 18926 is acid-sensing ion channel 3 (ASIC3/ACCN3) belonging to the ASIC family also known as DRASIC. The ASIC channels are proton-gated cation channels. These channels have been identified in sensory neurons and were implicated in mechanoreception and nociception. Due to its function and expression pattern, modulators of 18926 activity would modulate urinary bladder reflex and/or hyperreflexia. Modulators of 18926 would be useful in treating urological disorders, including but not limited to UI. 18926 polypeptides of the current invention would be useful in screening for modulators of 18926 activity.

30 **Gene ID 318**

[0066] The human 318 sequence (SEQ ID NO:58) is approximately 1670 nucleotides long including untranslated regions, contains a predicted methionine-initiated coding sequence of about 1107 nucleotides, including the termination codon (nucleotides indicated as coding of SEQ ID NO:58, SEQ ID NO:60). The coding sequence, located at

about nucleic acids 69 to 1175 of SEQ ID NO:58, encodes a 368 amino acid protein (SEQ ID NO:59).

[0067] 318 is a GPCR known as C-X-C chemokine receptor type 3 (CXCR-3 or CXC-R3). As assessed by TaqMan analysis, 318 mRNA showed high levels of expression in human uninfected peripheral blood leukocytes (PBL) followed by normal tonsil, lymph node, breast, ovary, colon tumors and BPH prostate. TaqMan analysis on the rat urology panel showed expression in spleen, followed by bladder, kidney, ovary, dorsal root ganglion (DRG), brain and spinal cord. Additional TaqMan analysis showed that 318 mRNA was upregulated in DRG in the aged and bladder outlet obstruction (BOO) rat models for UI.

[0068] Chemokine receptors are involved in neurological development, nociception and immune function. In nociception, they increase the sensitivity of neurons. Due to its function and expression pattern, modulating the activity of 318 would modulate the neuronal pathways involved in urinary function, bladder reflex and/or hyperreflexia. Modulators of 318 activity would be useful in treating urological disorders including but not limited to urinary incontinence. 318 polypeptides of the current invention would be useful in screening for modulators of 318 activity.

Gene ID 2058

[0069] The human 2058 sequence (SEQ ID NO:61) is approximately 3614 nucleotides long including untranslated regions, contains a predicted methionine-initiated coding sequence of about 2760 nucleotides, including the termination codon (nucleotides indicated as coding of SEQ ID NO:61, SEQ ID NO:63). The coding sequence, located at about nucleic acids 19 to 2778 of SEQ ID NO:61, encodes a 919 amino acid protein (SEQ ID NO:62).

[0070] 2058 is a ligand-gated cation channel known as ionotropic kainite 3 precursor (EAA5) or glutamate receptor 7 (GLUR7). As assessed by TaqMan analysis, 2058 mRNA showed high levels of expression in human brain followed by DRG, pituitary gland and spinal cord. TaqMan analysis on the rat urology panel showed restricted expression in brain, spinal cord and DRG.

[0071] Kainate receptors are known to be involved in synaptic transmission. Activating the receptors causes depolarization and increases neuronal activity. Due to its function and expression pattern, modulating the activity of 2058 would modulate the neuronal pathways involved in urinary function, bladder reflex and/or hyperreflexia.

Modulators of 2058 activity would be useful in treating urological disorders including but not limited to UI. 2058 polypeptides of the current invention would be useful in screening for modulators of 2058 activity.

5 **Gene ID 6351**

[0072] The human 6351 sequence (SEQ ID NO:64) is approximately 1380 nucleotides long including untranslated regions, contains a predicted methionine-initiated coding sequence of about 1260 nucleotides, including the termination codon (nucleotides indicated as coding of SEQ ID NO:64, SEQ ID NO:66). The coding sequence, located at
10 about nucleic acids 8 to 1267 of SEQ ID NO:64, encodes a 419 amino acid protein (SEQ ID NO:65).

[0073] 6351 is a carboxypeptidase known as carboxypeptidase A1 precursor (CPA1). As assessed by TaqMan analysis, 6351 mRNA was highly expressed in human pancreas followed by DRG and hypothalamus. TaqMan analysis on a rat urology panel
15 showed the highest expression in adrenal gland followed by colon, kidney, ovary, DRG, brain and spinal cord. Additional TaqMan analysis showed that 6351 mRNA was upregulated in DRG in the aged and spinal cord injury (SCI) rat models for UI.

[0074] The primary function of CPA1 is to breakdown peptides. Neuropeptides, enkephalins and opioids are known to reduce neuronal activity or block synaptic
20 transmission in DRG. Due to its function and expression pattern, modulating the activity of 6351 would modulate the activity and/or concentration of peptides in DRG affecting the neuronal pathways involved in urinary function, bladder reflex and/or hyperreflexia. Modulators of 6351 activity would be useful in treating urological disorders, including but not limited to UI. 6351 polypeptides of the current invention would be useful in screening
25 for modulators of 6351 activity.

[0075] Various aspects of the invention are described in further detail in the following subsections:

Screening Assays:

30 [0076] The invention provides a method (also referred to herein as a "screening assay") for identifying modulators, *i.e.*, candidate or test compounds or agents (*e.g.*, peptides, peptidomimetics, small molecules (organic or inorganic) or other drugs) which bind to 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 proteins, have a

stimulatory or inhibitory effect on, for example, 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 expression or 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 activity, or have a stimulatory or inhibitory effect on, for example, the expression or activity of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 substrate.

Compounds identified using the assays described herein may be useful for treating a urological disorder.

10 [0077] These assays are designed to identify compounds that bind to a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein, bind to other intracellular or extracellular proteins that interact with a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein, and interfere with the interaction of the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein with other intercellular or extracellular proteins. For example, in the case of the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein, which is a transmembrane receptor-type protein, such techniques can identify ligands for such a receptor. A 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein ligand or substrate can, for example, be used to ameliorate at least one symptom of a urological disorder. Such compounds may include, but are not limited to peptides, antibodies, or small organic or inorganic compounds. Such compounds may also include other cellular proteins.

20 [0078] Compounds identified via assays such as those described herein may be useful, for example, for treating a urological disorder. In instances whereby a urological disorder condition results from an overall lower level of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene expression and/or 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein in a cell or tissue, compounds that interact with the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303,

985, 13237, 13601, 18926, 318, 2058 or 6351 protein may include compounds which accentuate or amplify the activity of the bound 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein. Such compounds would bring about an effective increase in the
5 level of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein activity, thus ameliorating symptoms.

[0079] In other instances, mutations within the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601,
10 18926, 318, 2058 or 6351 gene may cause aberrant types or excessive amounts of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 proteins to be made which have a deleterious effect that leads to a urological disorder. Similarly, physiological conditions may cause an excessive increase in 1435, 559, 34021, 44099, 25278, 641, 260, 55089,
15 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene expression leading to a urological disorder. In such cases, compounds that bind to a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein may be identified that inhibit the activity of the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032,
20 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein. Assays for testing the effectiveness of compounds identified by techniques such as those described in this section are discussed herein.

[0080] In one embodiment, the invention provides assays for screening candidate or test compounds which are substrates of a 1435, 559, 34021, 44099, 25278, 641, 260,
25 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein or polypeptide or biologically active portion thereof. In another embodiment, the invention provides assays for screening candidate or test compounds which bind to or modulate the activity of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318,
30 2058 or 6351 protein or polypeptide or biologically active portion thereof. The test compounds of the present invention can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the 'one-bead one-compound' library method; and synthetic

library methods using affinity chromatography selection. The biological library approach is limited to peptide libraries, while the other four approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds (Lam, K.S. (1997) *Anticancer Drug Des.* 12:145).

- 5 [0081] Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt *et al.* (1993) *Proc. Natl. Acad. Sci. U.S.A.* 90:6909; Erb *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91:11422; Zuckermann *et al.* (1994). *J. Med. Chem.* 37:2678; Cho *et al.* (1993) *Science* 261:1303; Carrell *et al.* (1994) *Angew. Chem. Int. Ed. Engl.* 33:2059; Carell *et al.* (1994) *Angew. Chem. Int. Ed. Engl.* 33:2061; and in
10 Gallop *et al.* (1994) *J. Med. Chem.* 37:1233.

- [0082] Libraries of compounds may be presented in solution (*e.g.*, Houghten (1992) *Biotechniques* 13:412-421), or on beads (Lam (1991) *Nature* 354:82-84), chips (Fodor (1993) *Nature* 364:555-556), bacteria (Ladner USP 5,223,409), spores (Ladner USP '409), plasmids (Cull *et al.* (1992) *Proc Natl Acad Sci USA* 89:1865-1869) or on phage (Scott and
15 Smith (1990) *Science* 249:386-390); (Devlin (1990) *Science* 249:404-406); (Cwirla *et al.* (1990) *Proc. Natl. Acad. Sci.* 87:6378-6382); (Felici (1991) *J. Mol. Biol.* 222:301-310); (Ladner *supra.*).

- [0083] In one embodiment, an assay is a cell-based assay in which a cell which expresses a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656,
20 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein or biologically active portion thereof is contacted with a test compound and the ability of the test compound to modulate 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 activity is determined. Determining the ability of the test compound to modulate 1435,
25 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 activity can be accomplished by monitoring, for example, intracellular calcium, IP₃, cAMP, or diacylglycerol concentration, the phosphorylation profile of intracellular proteins, cell proliferation and/or migration, gene expression of, for example, cell surface adhesion molecules or genes associated with
30 UI and/r BPH, or the activity of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 -regulated transcription factor. The cell can be of mammalian origin, *e.g.*, a neural cell. In one embodiment, compounds that interact with a receptor domain can be screened for their ability to function as ligands, *i.e.*, to bind to the receptor and modulate a signal

transduction pathway. Identification of ligands, and measuring the activity of the ligand-receptor complex, leads to the identification of modulators (*e.g.*, antagonists) of this interaction. Such modulators may be useful in the treatment of a urological disorder.

[0084] The ability of the test compound to modulate 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 binding to a substrate or to bind to 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 can also be determined. Determining the ability of the test compound to modulate 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 binding to a substrate can be accomplished, for example, by coupling the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 substrate with a radioisotope or enzymatic label such that binding of the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 substrate to 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 can be determined by detecting the labeled 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 substrate in a complex. 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 could also be coupled with a radioisotope or enzymatic label to monitor the ability of a test compound to modulate 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 binding to a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 substrate in a complex. Determining the ability of the test compound to bind 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 can be accomplished, for example, by coupling the compound with a radioisotope or enzymatic label such that binding of the compound to 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 can be determined by detecting the labeled 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 compound in a complex. For example,

compounds (*e.g.*, 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 ligands or substrates) can be labeled with ^{125}I , ^{35}S , ^{14}C , or ^3H , either directly or indirectly, and the radioisotope detected by direct counting of radioemmission or by scintillation counting.

- 5 Compounds can further be enzymatically labeled with, for example, horseradish peroxidase, alkaline phosphatase, or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product.

[0085] It is also within the scope of this invention to determine the ability of a compound (*e.g.*, a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 10 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 ligand or substrate) to interact with 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 without the labeling of any of the interactants. For example, a microphysiometer can be used to detect the interaction of a compound with 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 15 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 without the labeling of either the compound or the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 (McConnell, H. M. *et al.* (1992) *Science* 257:1906-1912. As used herein, a "microphysiometer" (*e.g.*, Cytosensor) is an analytical instrument that measures 20 the rate at which a cell acidifies its environment using a light-addressable potentiometric sensor (LAPS). Changes in this acidification rate can be used as an indicator of the interaction between a compound and 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351.

25 [0086] In another embodiment, an assay is a cell-based assay comprising contacting a cell expressing a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 target molecule (*e.g.*, a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 substrate) with a 30 test compound and determining the ability of the test compound to modulate (*e.g.*, stimulate or inhibit) the activity of the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 target molecule. Determining the ability of the test compound to modulate the activity of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656,

62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 target molecule can be accomplished, for example, by determining the ability of the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein to bind to or interact with the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 target molecule.

[0087] Determining the ability of the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein or a biologically active fragment thereof, to bind to or interact with a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 target molecule can be accomplished by one of the methods described above for determining direct binding. In a preferred embodiment, determining the ability of the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein to bind to or interact with a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 target molecule can be accomplished by determining the activity of the target molecule. For example, the activity of the target molecule can be determined by detecting induction of a cellular second messenger of the target (*i.e.*, intracellular Ca^{2+} , diacylglycerol, IP_3 , cAMP), detecting catalytic/enzymatic activity of the target on an appropriate substrate, detecting the induction of a reporter gene (comprising a target-responsive regulatory element operatively linked to a nucleic acid encoding a detectable marker, *e.g.*, luciferase), or detecting a target-regulated cellular response (*e.g.*, gene expression).

[0088] In yet another embodiment, an assay of the present invention is a cell-free assay in which a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein or biologically active portion thereof, is contacted with a test compound and the ability of the test compound to bind to the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein or biologically active portion thereof is determined. Preferred biologically active portions of the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 proteins to be used in assays of the present invention include fragments which participate in interactions with

non-1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 molecules, *e.g.*, fragments with high surface probability scores. Binding of the test compound to the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein can be determined either directly or indirectly as described above. In a preferred embodiment, the assay includes contacting the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein or biologically active portion thereof with a known compound which binds 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein, wherein determining the ability of the test compound to interact with a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein comprises determining the ability of the test compound to preferentially bind to 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 or biologically active portion thereof as compared to the known compound. Compounds that modulate the interaction of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 with a known target protein may be useful in regulating the activity of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein, especially a mutant 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein.

[0089] In another embodiment, the assay is a cell-free assay in which a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein or biologically active portion thereof is contacted with a test compound and the ability of the test compound to modulate (*e.g.*, stimulate or inhibit) the activity of the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein or biologically active portion thereof is determined. Determining the ability

of the test compound to modulate the activity of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein can be accomplished, for example, by determining the ability of the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein to bind to a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 target molecule by one of the methods described above for determining direct binding. Determining the ability of the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein to bind to a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 target molecule can also be accomplished using a technology such as real-time Biomolecular Interaction Analysis (BIA) (Sjolander, S. and Urbaniczky, C. (1991) *Anal. Chem.* 63:2338-2345 and Szabo *et al.* (1995) *Curr. Opin. Struct. Biol.* 5:699-705). As used herein, "BIA" is a technology for studying biospecific interactions in real time, without labeling any of the interactants (*e.g.*, BIAcore). Changes in the optical phenomenon of surface plasmon resonance (SPR) can be used as an indication of real-time reactions between biological molecules.

[0090] In another embodiment, determining the ability of the test compound to modulate the activity of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein can be accomplished by determining the ability of the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein to further modulate the activity of a downstream effector of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 target molecule. For example, the activity of the effector molecule on an appropriate target can be determined or the binding of the effector to an appropriate target can be determined as previously described.

[0091] In yet another embodiment, the cell-free assay involves contacting a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein or biologically active portion thereof with a known compound which binds the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein to form an assay mixture, contacting the assay mixture with a

test compound, and determining the ability of the test compound to interact with the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein, wherein determining the ability of the test compound to interact with the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein comprises determining the ability of the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein to preferentially bind to or modulate the activity of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 target molecule.

[0092] In more than one embodiment of the above assay methods of the present invention, it may be desirable to immobilize either 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 or its target molecule to facilitate separation of complexed from uncomplexed forms of one or both of the proteins, as well as to accommodate automation of the assay. Binding of a test compound to a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein, or interaction of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein with a target molecule in the presence and absence of a candidate compound, can be accomplished in any vessel suitable for containing the reactants. Examples of such vessels include microtitre plates, test tubes, and micro-centrifuge tubes. In one embodiment, a fusion protein can be provided which adds a domain that allows one or both of the proteins to be bound to a matrix. For example, glutathione-S-transferase/1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 fusion proteins or glutathione-S-transferase/target fusion proteins can be adsorbed onto glutathione sepharose beads (Sigma Chemical, St. Louis, MO) or glutathione derivatized microtitre plates, which are then combined with the test compound or the test compound and either the non-adsorbed target protein or 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein, and the mixture incubated under conditions conducive to complex formation (*e.g.*, at physiological conditions for salt and pH). Following incubation, the beads or microtitre plate wells are washed to remove any unbound components, the matrix immobilized in the case of beads,

complex determined either directly or indirectly, for example, as described above.

Alternatively, the complexes can be dissociated from the matrix, and the level of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 binding or activity determined using standard techniques.

[0093] Other techniques for immobilizing proteins on matrices can also be used in the screening assays of the invention. For example, either a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein or a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 target molecule can be immobilized utilizing conjugation of biotin and streptavidin. Biotinylated 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein or target molecules can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques known in the art (*e.g.*, biotinylation kit, Pierce Chemicals, Rockford, IL), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical).

Alternatively, antibodies reactive with 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein or target molecules but which do not interfere with binding of the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein to its target molecule can be derivatized to the wells of the plate, and unbound target or 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein trapped in the wells by antibody conjugation.

Methods for detecting such complexes, in addition to those described above for the GST-immobilized complexes, include immunodetection of complexes using antibodies reactive with the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein or target molecule, as well as enzyme-linked assays which rely on detecting an enzymatic activity associated with the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein or target molecule.

[0094] In another embodiment, modulators of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 expression are identified in a method wherein a cell is contacted

with a candidate compound and the expression of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 mRNA or protein in the cell is determined. The level of expression of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 mRNA or protein in the presence of the candidate compound is compared to the level of expression of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 mRNA or protein in the absence of the candidate compound. The candidate compound can then be identified as a modulator of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 expression based on this comparison. For example, when expression of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 mRNA or protein is greater (statistically significantly greater) in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 mRNA or protein expression. Alternatively, when expression of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 mRNA or protein is less (statistically significantly less) in the presence of the candidate compound than in its absence, the candidate compound is identified as an inhibitor of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 mRNA or protein expression. The level of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 mRNA or protein expression in the cells can be determined by methods described herein for detecting 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 mRNA or protein.

[0095] In yet another aspect of the invention, the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 proteins can be used as "bait proteins" in a two-hybrid assay or three-hybrid assay (see, e.g., U.S. Patent No. 5,283,317; Zervos *et al.* (1993) *Cell* 72:223-232; Madura *et al.* (1993) *J. Biol. Chem.* 268:12046-12054; Bartel *et al.* (1993) *Biotechniques* 14:920-924; Iwabuchi *et al.* (1993) *Oncogene* 8:1693-1696; and Brent

WO94/10300), to identify other proteins, which bind to or interact with 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 ("1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 -binding proteins" or "1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 -bp") and are involved in 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 activity. Such 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 -binding proteins are also likely to be involved in the propagation of signals by the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 proteins or 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 targets as, for example, downstream elements of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 -mediated signaling pathway. Alternatively, such 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 -binding proteins are likely to be 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 inhibitors.

[0096] The two-hybrid system is based on the modular nature of most transcription factors, which consist of separable DNA-binding and activation domains. Briefly, the assay utilizes two different DNA constructs. In one construct, the gene that codes for a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein is fused to a gene encoding the DNA binding domain of a known transcription factor (*e.g.*, GAL-4). In the other construct, a DNA sequence, from a library of DNA sequences, that encodes an unidentified protein ("prey" or "sample") is fused to a gene that codes for the activation domain of the known transcription factor. If the "bait" and the "prey" proteins are able to interact, *in vivo*, forming a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 -dependent complex, the DNA-binding and activation domains of the transcription factor are brought into close proximity. This proximity allows transcription of a reporter gene (*e.g.*, LacZ) which is

operably linked to a transcriptional regulatory site responsive to the transcription factor. Expression of the reporter gene can be detected and cell colonies containing the functional transcription factor can be isolated and used to obtain the cloned gene which encodes the protein which interacts with the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein.

[0097] In another aspect, the invention pertains to a combination of two or more of the assays described herein. For example, a modulating agent can be identified using a cell-based or a cell free assay, and the ability of the agent to modulate the activity of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein can be confirmed *in vivo*, e.g., in an animal such as an animal model for a urological disorder, as described herein.

[0098] This invention further pertains to novel agents identified by the above-described screening assays. Accordingly, it is within the scope of this invention to further use an agent identified as described herein in an appropriate animal model. For example, an agent identified as described herein (e.g., a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 modulating agent, an antisense 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 nucleic acid molecule, a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 -specific antibody, or a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 -binding partner) can be used in an animal model to determine the efficacy, toxicity, or side effects of treatment with such an agent. Alternatively, an agent identified as described herein can be used in an animal model to determine the mechanism of action of such an agent. Furthermore, this invention pertains to uses of novel agents identified by the above-described screening assays for treatments as described herein.

[0099] Any of the compounds, including but not limited to compounds such as those identified in the foregoing assay systems, may be tested for the ability to ameliorate at least one symptom of a urological disorder. Cell-based and animal model-based assays for the identification of compounds exhibiting such an ability to ameliorate at least one symptom of a urological disorder are described herein.

[00100] In addition, animal-based models of a urological disorder, such as those described herein, may be used to identify compounds capable of treating a urological disorder. Such animal models may be used as test substrates for the identification of drugs, pharmaceuticals, therapies, and interventions which may be effective in treating a urological disorder. For example, animal models may be exposed to a compound, suspected of exhibiting an ability to treat a urological disorder, at a sufficient concentration and for a time sufficient to elicit such an amelioration of at least one symptom of a urological disorder in the exposed animals. The response of the animals to the exposure may be monitored by assessing the reversal of the symptoms of a urological disorder before and after treatment.

[00101] With regard to intervention, any treatments which reverse any aspect of a urological disorder (i.e. have an effect on UI and/or BPH) should be considered as candidates for a human urological disorder therapeutic intervention. Dosages of test agents may be determined by deriving dose-response curves.

[00102] Additionally, gene expression patterns may be utilized to assess the ability of a compound to ameliorate at least one symptom of a urological disorder. For example, the expression pattern of one or more genes may form part of a "gene expression profile" or "transcriptional profile" which may be then be used in such an assessment. "Gene expression profile" or "transcriptional profile", as used herein, includes the pattern of mRNA expression obtained for a given tissue or cell type under a given set of conditions. Gene expression profiles may be generated, for example, by utilizing a differential display procedure, Northern analysis and/or RT-PCR. In one embodiment, 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene sequences may be used as probes and/or PCR primers for the generation and corroboration of such gene expression profiles.

[00103] Gene expression profiles may be characterized for known states, either cardiovascular disease or normal, within the cell- and/or animal-based model systems. Subsequently, these known gene expression profiles may be compared to ascertain the effect a test compound has to modify such gene expression profiles, and to cause the profile to more closely resemble that of a more desirable profile.

[00104] For example, administration of a compound may cause the gene expression profile of a urological disorder disease model system to more closely resemble the control system. Administration of a compound may, alternatively, cause the gene expression profile of a control system to begin to mimic a urological disorder or a urological disorder

disease state. Such a compound may, for example, be used in further characterizing the compound of interest, or may be used in the generation of additional animal models.

Cell- and Animal-Based Model Systems

5 [00105] Described herein are cell- and animal-based systems which act as models for urological disorder. These systems may be used in a variety of applications. For example, the cell- and animal-based model systems may be used to further characterize differentially expressed genes associated with a urological disorder, *e.g.*, 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 10 13237, 13601, 18926, 318, 2058 or 6351. In addition, animal- and cell-based assays may be used as part of screening strategies designed to identify compounds which are capable of ameliorating at least one symptom of a urological disorder, as described, below. Thus, the animal- and cell-based models may be used to identify drugs, pharmaceuticals, therapies and interventions which may be effective in treating a urological disorder. Furthermore, 15 such animal models may be used to determine the LD50 and the ED50 in animal subjects, and such data can be used to determine the *in vivo* efficacy of potential urological disorder treatments.

Animal-Based Systems

20 [00106] Animal-based model systems of urological disorder may include, but are not limited to, non-recombinant and engineered transgenic animals.

[00107] Non-recombinant animal models for urological disorder may include, for example, genetic models.

[00108] Additionally, animal models exhibiting a urological disorder may be 25 engineered by using, for example, 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene sequences described above, in conjunction with techniques for producing transgenic animals that are well known to those of skill in the art. For example, 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 30 985, 13237, 13601, 18926, 318, 2058 or 6351 gene sequences may be introduced into, and overexpressed in, the genome of the animal of interest, or, if endogenous 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene sequences are present, they may either be overexpressed or, alternatively, be disrupted in order to underexpress or inactivate 1435,

559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene expression.

[00109] The host cells of the invention can also be used to produce non-human transgenic animals. For example, in one embodiment, a host cell of the invention is a fertilized oocyte or an embryonic stem cell into which 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 -coding sequences have been introduced. Such host cells can then be used to create non-human transgenic animals in which exogenous 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 sequences have been introduced into their genome or homologous recombinant animals in which endogenous 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 sequences have been altered. Such animals are useful for studying the function and/or activity of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 and for identifying and/or evaluating modulators of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 activity. As used herein, a "transgenic animal" is a non-human animal, preferably a mammal, more preferably a rodent such as a rat or mouse, in which one or more of the cells of the animal includes a transgene. Other examples of transgenic animals include non-human primates, sheep, dogs, cows, goats, chickens, amphibians, and the like. A transgene is exogenous DNA which is integrated into the genome of a cell from which a transgenic animal develops and which remains in the genome of the mature animal, thereby directing the expression of an encoded gene product in one or more cell types or tissues of the transgenic animal. As used herein, a "homologous recombinant animal" is a non-human animal, preferably a mammal, more preferably a mouse, in which an endogenous 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene has been altered by homologous recombination between the endogenous gene and an exogenous DNA molecule introduced into a cell of the animal, *e.g.*, an embryonic cell of the animal, prior to development of the animal.

[00110] A transgenic animal used in the methods of the invention can be created by introducing a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 -encoding nucleic

acid into the male pronuclei of a fertilized oocyte, *e.g.*, by microinjection, retroviral infection, and allowing the oocyte to develop in a pseudopregnant female foster animal. The 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 cDNA sequence can be

5 introduced as a transgene into the genome of a non-human animal. Alternatively, a nonhuman homologue of a human 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene, such as a mouse or rat 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or

10 6351 gene, can be used as a transgene. Alternatively, a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene homologue, such as another 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 family member, can be isolated based on hybridization to

15 the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 cDNA sequences and used as a transgene. Intronic sequences and polyadenylation signals can also be included in the transgene to increase the efficiency of expression of the transgene. A tissue-specific regulatory sequence(s) can be operably linked to a 1435, 559, 34021, 44099, 25278, 641,

20 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 transgene to direct expression of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein to particular cells. Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice,

25 have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009, both by Leder *et al.*, U.S. Patent No. 4,873,191 by Wagner *et al.* and in Hogan, B., *Manipulating the Mouse Embryo*, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986). Similar methods are used for production of other transgenic animals. A transgenic founder animal can be identified based upon the presence

30 of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 transgene in its genome and/or expression of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 mRNA in tissues or cells of the animals. A transgenic founder animal can then be used to breed additional

animals carrying the transgene. Moreover, transgenic animals carrying a transgene encoding a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein can further be bred to other transgenic animals carrying other transgenes.

5 [00111] To create a homologous recombinant animal, a vector is prepared which contains at least a portion of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene into which a deletion, addition or substitution has been introduced to thereby alter, *e.g.*, functionally disrupt, the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 10 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene. The 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene can be a human gene but more preferably, is a non-human homologue of a human 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 15 318, 2058 or 6351 gene. For example, a rat 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene can be used to construct a homologous recombination nucleic acid molecule, *e.g.*, a vector, suitable for altering an endogenous 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 20 13601, 18926, 318, 2058 or 6351 gene in the mouse genome. In a preferred embodiment, the homologous recombination nucleic acid molecule is designed such that, upon homologous recombination, the endogenous 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene is functionally disrupted (*i.e.*, no longer encodes a functional protein; 25 also referred to as a "knock out" vector). Alternatively, the homologous recombination nucleic acid molecule can be designed such that, upon homologous recombination, the endogenous 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene is mutated or otherwise altered but still encodes functional protein (*e.g.*, the upstream regulatory region 30 can be altered to thereby alter the expression of the endogenous 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein). In the homologous recombination nucleic acid molecule, the altered portion of the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or

6351 gene is flanked at its 5' and 3' ends by additional nucleic acid sequence of the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene to allow for homologous recombination to occur between the exogenous 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene carried by the homologous recombination nucleic acid molecule and an endogenous 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene in a cell, *e.g.*, an embryonic stem cell. The additional flanking 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 nucleic acid sequence is of sufficient length for successful homologous recombination with the endogenous gene. Typically, several kilobases of flanking DNA (both at the 5' and 3' ends) are included in the homologous recombination nucleic acid molecule (see, *e.g.*, Thomas, K.R. and Capecchi, M. R. (1987) *Cell* 51:503 for a description of homologous recombination vectors). The homologous recombination nucleic acid molecule is introduced into a cell, *e.g.*, an embryonic stem cell line (*e.g.*, by electroporation) and cells in which the introduced 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene has homologously recombined with the endogenous 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene are selected (see *e.g.*, Li, E. *et al.* (1992) *Cell* 69:915). The selected cells can then injected into a blastocyst of an animal (*e.g.*, a mouse) to form aggregation chimeras (see *e.g.*, Bradley, A. in *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, E.J. Robertson, ed. (IRL, Oxford, 1987) pp. 113-152). A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term. Progeny harboring the homologously recombined DNA in their germ cells can be used to breed animals in which all cells of the animal contain the homologously recombined DNA by germline transmission of the transgene. Methods for constructing homologous recombination nucleic acid molecules, *e.g.*, vectors, or homologous recombinant animals are described further in Bradley, A. (1991) *Current Opinion in Biotechnology* 2:823-829 and in PCT International Publication Nos.: WO 90/11354 by Le Mouellec *et al.*; WO 91/01140 by Smithies *et al.*; WO 92/0968 by Zijlstra *et al.*; and WO 93/04169 by Berns *et al.*

[00112] In another embodiment, transgenic non-human animals for use in the methods of the invention can be produced which contain selected systems which allow for regulated expression of the transgene. One example of such a system is the *cre/loxP* recombinase system of bacteriophage P1. For a description of the *cre/loxP* recombinase system, see, *e.g.*, Lakso *et al.* (1992) *Proc. Natl. Acad. Sci. USA* 89:6232-6236. Another example of a recombinase system is the FLP recombinase system of *Saccharomyces cerevisiae* (O'Gorman *et al.* (1991) *Science* 251:1351-1355. If a *cre/loxP* recombinase system is used to regulate expression of the transgene, animals containing transgenes encoding both the *Cre* recombinase and a selected protein are required. Such animals can be provided through the construction of "double" transgenic animals, *e.g.*, by mating two transgenic animals, one containing a transgene encoding a selected protein and the other containing a transgene encoding a recombinase.

[00113] Clones of the non-human transgenic animals described herein can also be produced according to the methods described in Wilmut, I. *et al.* (1997) *Nature* 385:810-813 and PCT International Publication Nos. WO 97/07668 and WO 97/07669. In brief, a cell, *e.g.*, a somatic cell, from the transgenic animal can be isolated and induced to exit the growth cycle and enter G₀ phase. The quiescent cell can then be fused, *e.g.*, through the use of electrical pulses, to an enucleated oocyte from an animal of the same species from which the quiescent cell is isolated. The reconstructed oocyte is then cultured such that it develops to morula or blastocyte and then transferred to pseudopregnant female foster animal. The offspring borne of this female foster animal will be a clone of the animal from which the cell, *e.g.*, the somatic cell, is isolated.

[00114] The 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 transgenic animals that express 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 mRNA or a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 peptide (detected immunocytochemically, using antibodies directed against 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 epitopes) at easily detectable levels should then be further evaluated to identify those animals which display a characteristic urological disorder.

Cell-Based Systems

[00115] Cells that contain and express 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene sequences which encode a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein, and, further, exhibit cellular phenotypes associated with BPH and/or UI, may be used to identify compounds that exhibit an effect on a urological disorder. Such cells may include non-recombinant monocyte cell lines, such as U937 (ATCC# CRL-1593), THP-1 (ATCC#TIB-202), and P388D1 (ATCC# TIB-63); endothelial cells such as human umbilical vein endothelial cells (HUVECs), human microvascular endothelial cells (HMVEC), and bovine aortic endothelial cells (BAECs); as well as generic mammalian cell lines such as HeLa cells and COS cells, *e.g.*, COS-7 (ATCC# CRL-1651), prostate and bladder cell lines.. Further, such cells may include recombinant, transgenic cell lines. For example, the urological disorder animal models of the invention, discussed above, may be used to generate cell lines, containing one or more cell types involved in BPH and/or UI, that can be used as cell culture models for this disorder. While primary cultures derived from the urological disorder model transgenic animals of the invention may be utilized, the generation of continuous cell lines is preferred. For examples of techniques which may be used to derive a continuous cell line from the transgenic animals, see Small *et al.*, (1985) *Mol. Cell Biol.* 5:642-648.

[00116] Alternatively, cells of a cell type known to be involved in BPH and/or UI may be transfected with sequences capable of increasing or decreasing the amount of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene expression within the cell. For example, 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene sequences may be introduced into, and overexpressed in, the genome of the cell of interest, or, if endogenous 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene sequences are present, they may be either overexpressed or, alternatively disrupted in order to underexpress or inactivate 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene expression.

[00117] In order to overexpress a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or

6351 gene, the coding portion of the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene may be ligated to a regulatory sequence which is capable of driving gene expression in the cell type of interest, *e.g.*, an endothelial cell. Such regulatory regions will be well known to those of skill in the art, and may be utilized in the absence of undue experimentation. Recombinant methods for expressing target genes are described above.

[00118] For underexpression of an endogenous 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene sequence, such a sequence may be isolated and engineered such that when reintroduced into the genome of the cell type of interest, the endogenous 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 alleles will be inactivated.

Preferably, the engineered 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 sequence is introduced via gene targeting such that the endogenous 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 sequence is disrupted upon integration of the engineered 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 sequence into the cell's genome. Transfection of host cells with 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 genes is discussed, above.

[00119] Cells treated with compounds or transfected with 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 genes can be examined for phenotypes associated with BPH and/or UI.

[00120] Transfection of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 nucleic acid may be accomplished by using standard techniques (described in, for example, Ausubel (1989) *supra*). Transfected cells should be evaluated for the presence of the recombinant 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene sequences, for expression and accumulation of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351

mRNA, and for the presence of recombinant 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein production. In instances wherein a decrease in 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene expression is desired, standard techniques may be used to demonstrate whether a decrease in endogenous 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene expression and/or in 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein production is achieved.

Predictive Medicine:

[00121] The present invention also pertains to the field of predictive medicine in which diagnostic assays, prognostic assays, and monitoring clinical trials are used for prognostic (predictive) purposes to thereby treat an individual prophylactically. Accordingly, one aspect of the present invention relates to diagnostic assays for determining 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein and/or nucleic acid expression as well as 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 activity, in the context of a biological sample (*e.g.*, blood, serum, cells, *e.g.*, endothelial cells, or tissue, *e.g.*, vascular tissue, bladder tissue or prostate tissue) to thereby determine whether an individual is afflicted with a predisposition or is experiencing a urological disorder. The invention also provides for prognostic (or predictive) assays for determining whether an individual is at risk of developing a urological disorder. For example, mutations in a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene can be assayed for in a biological sample. Such assays can be used for prognostic or predictive purpose to thereby prophylactically treat an individual prior to the onset of a urological disorder.

[00122] Another aspect of the invention pertains to monitoring the influence of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 modulators (*e.g.*, anti-1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303,

985, 13237, 13601, 18926, 318, 2058 or 6351 antibodies or 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 ribozymes) on the expression or activity of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 in clinical trials.

[00123] These and other agents are described in further detail in the following sections.

Diagnostic Assays

10 [00124] To determine whether a subject is afflicted with a disease, a biological sample may be obtained from a subject and the biological sample may be contacted with a compound or an agent capable of detecting a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein or nucleic acid (e.g., mRNA or genomic DNA) that encodes a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein, in the biological sample. A preferred agent for detecting 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 mRNA or genomic DNA is a labeled nucleic acid probe capable of hybridizing to 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 mRNA or genomic DNA. The nucleic acid probe can be, for example, the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 nucleic acid set forth in SEQ ID NO:1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61 and 64 or a portion thereof, such as an oligonucleotide of at least 15, 20, 25, 30, 35, 40, 45, 50, 100, 250 or 500 nucleotides in length and sufficient to specifically hybridize under stringent conditions to 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 mRNA or genomic DNA. Other suitable probes for use in the diagnostic assays of the invention are described herein.

[00125] A preferred agent for detecting 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein in a sample is an antibody capable of binding to 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985,

13237, 13601, 18926, 318, 2058 or 6351 protein, preferably an antibody with a detectable label. Antibodies can be polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment thereof (*e.g.*, Fab or F(ab')₂) can be used. The term "labeled", with regard to the probe or antibody, is intended to encompass direct labeling of the probe or antibody by coupling (*i.e.*, physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with fluorescently labeled streptavidin.

10 [00126] The term "biological sample" is intended to include tissues, cells, and biological fluids isolated from a subject, as well as tissues, cells, and fluids present within a subject. That is, the detection method of the invention can be used to detect 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 mRNA, protein, or genomic DNA in a
15 biological sample *in vitro* as well as *in vivo*. For example, *in vitro* techniques for detection of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 mRNA include Northern hybridizations and *in situ* hybridizations. *In vitro* techniques for detection of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein include enzyme linked
20 immunosorbent assays (ELISAs), Western blots, immunoprecipitations and immunofluorescence. *In vitro* techniques for detection of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 genomic DNA include Southern hybridizations. Furthermore, *in vivo* techniques for detection of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351
25 protein include introducing into a subject a labeled anti-1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 antibody. For example, the antibody can be labeled with a
30 radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

[00127] In another embodiment, the methods further involve obtaining a control biological sample from a control subject, contacting the control sample with a compound or agent capable of detecting 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407,

42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein, mRNA, or genomic DNA, such that the presence of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein, mRNA or genomic DNA is detected in the biological sample, and comparing the presence of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein, mRNA or genomic DNA in the control sample with the presence of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein, mRNA or genomic DNA in the test sample.

Prognostic Assays

[00128] The present invention further pertains to methods for identifying subjects having or at risk of developing a disease associated with aberrant 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 expression or activity.

[00129] As used herein, the term "aberrant" includes a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 expression or activity which deviates from the wild type 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 expression or activity. Aberrant expression or activity includes increased or decreased expression or activity, as well as expression or activity which does not follow the wild type developmental pattern of expression or the subcellular pattern of expression. For example, aberrant 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 expression or activity is intended to include the cases in which a mutation in the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene causes the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene to be under-expressed or over-expressed and situations in which such mutations result in a non-functional 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein or a protein which does not function in a wild-type fashion, e.g., a protein which does not interact with a 1435,

559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 substrate, or one which interacts with a non-1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 substrate.

- 5 **[00130]** The assays described herein, such as the preceding diagnostic assays or the following assays, can be used to identify a subject having or at risk of developing a disease. A biological sample may be obtained from a subject and tested for the presence or absence of a genetic alteration. For example, such genetic alterations can be detected by ascertaining the existence of at least one of 1) a deletion of one or more nucleotides from a
- 10 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene, 2) an addition of one or more nucleotides to a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene, 3) a substitution of one or more nucleotides of a 1435, 559, 34021, 44099, 25278, 641, 260,
- 15 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene, 4) a chromosomal rearrangement of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene, 5) an alteration in the level of a messenger RNA transcript of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302,
- 20 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene, 6) aberrant modification of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene, such as of the methylation pattern of the genomic DNA, 7) the presence of a non-wild type splicing pattern of a messenger RNA transcript of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407,
- 25 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene, 8) a non-wild type level of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 -protein, 9) allelic loss of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene,
- 30 and 10) inappropriate post-translational modification of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 -protein.

[00131] As described herein, there are a large number of assays known in the art which can be used for detecting genetic alterations in a 1435, 559, 34021, 44099, 25278,

641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene. For example, a genetic alteration in a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene may be detected using a probe/primer in a
5 polymerase chain reaction (PCR) (see, *e.g.*, U.S. Patent Nos. 4,683,195 and 4,683,202), such as anchor PCR or RACE PCR, or, alternatively, in a ligation chain reaction (LCR) (see, *e.g.*, Landegran *et al.* (1988) *Science* 241:1077-1080; and Nakazawa *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91:360-364), the latter of which can be particularly useful for detecting point mutations in a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407,
10 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene (see Abravaya *et al.* (1995) *Nucleic Acids Res.* 23:675-682). This method includes collecting a biological sample from a subject, isolating nucleic acid (*e.g.*, genomic DNA, mRNA or both) from the sample, contacting the nucleic acid sample with one or more primers which specifically hybridize to a 1435, 559, 34021, 44099, 25278, 641, 260,
15 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene under conditions such that hybridization and amplification of the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene (if present) occurs, and detecting the presence or absence of an amplification product, or detecting the size of the
20 amplification product and comparing the length to a control sample. It is anticipated that PCR and/or LCR may be desirable to use as a preliminary amplification step in conjunction with any of the techniques used for detecting mutations described herein.

[00132] Alternative amplification methods include: self sustained sequence replication (Guatelli, J.C. *et al.* (1990) *Proc. Natl. Acad. Sci. USA* 87:1874-1878),
25 transcriptional amplification system (Kwoh, D.Y. *et al.* (1989) *Proc. Natl. Acad. Sci. USA* 86:1173-1177), Q-Beta Replicase (Lizardi, P.M. *et al.* (1988) *Bio-Technology* 6:1197), or any other nucleic acid amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules
30 are present in very low numbers.

[00133] In an alternative embodiment, mutations in a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene from a biological sample can be identified by alterations in restriction enzyme cleavage patterns. For example, sample and control DNA

is isolated, amplified (optionally), digested with one or more restriction endonucleases, and fragment length sizes are determined by gel electrophoresis and compared. Differences in fragment length sizes between sample and control DNA indicates mutations in the sample DNA. Moreover, the use of sequence specific ribozymes (see, for example, U.S. Patent
5 No. 5,498,531) can be used to score for the presence of specific mutations by development or loss of a ribozyme cleavage site.

[00134] In other embodiments, genetic mutations in 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 can be identified by hybridizing biological sample
10 derived and control nucleic acids, *e.g.*, DNA or RNA, to high density arrays containing hundreds or thousands of oligonucleotide probes (Cronin, M.T. *et al.* (1996) *Human Mutation* 7:244-255; Kozal, M.J. *et al.* (1996) *Nature Medicine* 2:753-759). For example, genetic mutations in 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 can be
15 identified in two dimensional arrays containing light-generated DNA probes as described in Cronin, M.T. *et al.* (1996) *supra*. Briefly, a first hybridization array of probes can be used to scan through long stretches of DNA in a sample and control to identify base changes between the sequences by making linear arrays of sequential, overlapping probes. This step allows for the identification of point mutations. This step is followed by a second
20 hybridization array that allows for the characterization of specific mutations by using smaller, specialized probe arrays complementary to all variants or mutations detected. Each mutation array is composed of parallel probe sets, one complementary to the wild-type gene and the other complementary to the mutant gene.

[00135] In yet another embodiment, any of a variety of sequencing reactions known
25 in the art can be used to directly sequence the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene in a biological sample and detect mutations by comparing the sequence of the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 in the biological sample
30 with the corresponding wild-type (control) sequence. Examples of sequencing reactions include those based on techniques developed by Maxam and Gilbert (1977) *Proc. Natl. Acad. Sci. USA* 74:560 or Sanger (1977) *Proc. Natl. Acad. Sci. USA* 74:5463). It is also contemplated that any of a variety of automated sequencing procedures can be utilized when performing the diagnostic assays (Naeve, C. W. (1995) *Biotechniques* 19:448-53),

including sequencing by mass spectrometry (see, *e.g.*, PCT International Publication No. WO 94/16101; Cohen *et al.* (1996) *Adv. Chromatogr.* 36:127-162; and Griffin *et al.* (1993) *Appl. Biochem. Biotechnol.* 38:147-159).

[00136] Other methods for detecting mutations in the 1435, 559, 34021, 44099, 5 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene include methods in which protection from cleavage agents is used to detect mismatched bases in RNA/RNA or RNA/DNA heteroduplexes (Myers *et al.* (1985) *Science* 230:1242). In general, the art technique of "mismatch cleavage" starts by providing heteroduplexes formed by hybridizing (labeled) RNA or 10 DNA containing the wild-type 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 sequence with potentially mutant RNA or DNA obtained from a tissue sample. The double-stranded duplexes are treated with an agent which cleaves single-stranded regions of the duplex such as which will exist due to basepair mismatches between the control and 15 sample strands. For instance, RNA/DNA duplexes can be treated with RNase and DNA/DNA hybrids treated with S1 nuclease to enzymatically digest the mismatched regions. In other embodiments, either DNA/DNA or RNA/DNA duplexes can be treated with hydroxylamine or osmium tetroxide and with piperidine in order to digest mismatched regions. After digestion of the mismatched regions, the resulting material is then separated 20 by size on denaturing polyacrylamide gels to determine the site of mutation. See, for example, Cotton *et al.* (1988) *Proc. Natl Acad Sci USA* 85:4397 and Saleeba *et al.* (1992) *Methods Enzymol.* 217:286-295. In a preferred embodiment, the control DNA or RNA can be labeled for detection.

[00137] In still another embodiment, the mismatch cleavage reaction employs one or 25 more proteins that recognize mismatched base pairs in double-stranded DNA (so called "DNA mismatch repair" enzymes) in defined systems for detecting and mapping point mutations in 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 cDNAs obtained from samples of cells. For example, the mutY enzyme of *E. coli* cleaves A at G/A 30 mismatches and the thymidine DNA glycosylase from HeLa cells cleaves T at G/T mismatches (Hsu *et al.* (1994) *Carcinogenesis* 15:1657-1662). According to an exemplary embodiment, a probe based on a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 sequence, *e.g.*, a wild-type 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407,

42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 sequence, is hybridized to a cDNA or other DNA product from a test cell(s). The duplex is treated with a DNA mismatch repair enzyme, and the cleavage products, if any, can be detected from electrophoresis protocols or the like. See, for example, U.S. Patent No.

5 5,459,039.

[00138] In other embodiments, alterations in electrophoretic mobility will be used to identify mutations in 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 genes. For example, single strand conformation polymorphism (SSCP) may be used to detect

10 differences in electrophoretic mobility between mutant and wild type nucleic acids (Orita *et al.* (1989) *Proc Natl. Acad. Sci USA*: 86:2766; see also Cotton (1993) *Mutat. Res.* 285:125-144 and Hayashi (1992) *Genet. Anal. Tech. Appl.* 9:73-79). Single-stranded DNA fragments of sample and control 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351

15 nucleic acids will be denatured and allowed to renature. The secondary structure of single-stranded nucleic acids varies according to sequence, the resulting alteration in electrophoretic mobility enables the detection of even a single base change. The DNA fragments may be labeled or detected with labeled probes. The sensitivity of the assay may be enhanced by using RNA (rather than DNA), in which the secondary structure is more
20 sensitive to a change in sequence. In a preferred embodiment, the subject method utilizes heteroduplex analysis to separate double stranded heteroduplex molecules on the basis of changes in electrophoretic mobility (Keen *et al.* (1991) *Trends Genet* 7:5).

[00139] In yet another embodiment the movement of mutant or wild-type fragments in polyacrylamide gels containing a gradient of denaturant is assayed using denaturing
25 gradient gel electrophoresis (DGGE) (Myers *et al.* (1985) *Nature* 313:495). When DGGE is used as the method of analysis, DNA will be modified to ensure that it does not completely denature, for example by adding a GC clamp of approximately 40 bp of high-melting GC-rich DNA by PCR. In a further embodiment, a temperature gradient is used in place of a denaturing gradient to identify differences in the mobility of control and sample
30 DNA (Rosenbaum and Reissner (1987) *Biophys Chem* 265:12753).

[00140] Examples of other techniques for detecting point mutations include, but are not limited to, selective oligonucleotide hybridization, selective amplification, or selective primer extension. For example, oligonucleotide primers may be prepared in which the known mutation is placed centrally and then hybridized to target DNA under conditions

which permit hybridization only if a perfect match is found (Saiki *et al.* (1986) *Nature* 324:163); Saiki *et al.* (1989) *Proc. Natl Acad. Sci USA* 86:6230). Such allele specific oligonucleotides are hybridized to PCR amplified target DNA or a number of different mutations when the oligonucleotides are attached to the hybridizing membrane and
5 hybridized with labeled target DNA.

[00141] Alternatively, allele specific amplification technology which depends on selective PCR amplification may be used in conjunction with the instant invention. Oligonucleotides used as primers for specific amplification may carry the mutation of interest in the center of the molecule (so that amplification depends on differential
10 hybridization) (Gibbs *et al.* (1989) *Nucleic Acids Res.* 17:2437-2448) or at the extreme 3' end of one primer where, under appropriate conditions, mismatch can prevent, or reduce polymerase extension (Prossner (1993) *Tibtech* 11:238). In addition it may be desirable to introduce a novel restriction site in the region of the mutation to create cleavage-based detection (Gasparini *et al.* (1992) *Mol. Cell Probes* 6:1). It is anticipated that in certain
15 embodiments amplification may also be performed using Taq ligase for amplification (Barany (1991) *Proc. Natl. Acad. Sci USA* 88:189). In such cases, ligation will occur only if there is a perfect match at the 3' end of the 5' sequence making it possible to detect the presence of a known mutation at a specific site by looking for the presence or absence of amplification.

20 [00142] Furthermore, the prognostic assays described herein can be used to determine whether a subject can be administered a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 modulator (*e.g.*, an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, or small molecule) to effectively treat a disease.

Monitoring of Effects During Clinical Trials

[00143] The present invention further provides methods for determining the effectiveness of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 modulator (*e.g.*, a
30 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 modulator identified herein) in treating a disease. For example, the effectiveness of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 modulator in increasing 1435, 559, 34021, 44099, 25278, 641,

260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene expression, protein levels, or in upregulating 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 activity, can be monitored in clinical trials of subjects exhibiting decreased 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene expression, protein levels, or downregulated 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 activity. Alternatively, the effectiveness of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 modulator in decreasing 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene expression, protein levels, or in downregulating 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 activity, can be monitored in clinical trials of subjects exhibiting increased 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene expression, protein levels, or 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 activity. In such clinical trials, the expression or activity of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene, and preferably, other genes that have been implicated in nociception can be used as a "read out" or marker of the phenotype of a particular cell.

[00144] For example, and not by way of limitation, genes, including 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351, that are modulated in cells by treatment with an agent which modulates 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 activity (*e.g.*, identified in a screening assay as described herein) can be identified. Thus, to study the effect of agents which modulate 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 activity on subjects suffering from a urological disorder in, for example, a clinical trial, cells can be isolated and RNA prepared and analyzed for the levels of

expression of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 and other genes implicated in the urological disorder. The levels of gene expression (*e.g.*, a gene expression pattern) can be quantified by Northern blot analysis or RT-PCR, as described
5 herein, or alternatively by measuring the amount of protein produced, by one of the methods described herein, or by measuring the levels of activity of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 or other genes. In this way, the gene expression pattern can serve as a marker, indicative of the physiological response of the cells to the
10 agent which modulates 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 activity. This response state may be determined before, and at various points during treatment of the individual with the agent which modulates 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318,
15 2058 or 6351 activity.

[00145] In a preferred embodiment, the present invention provides a method for monitoring the effectiveness of treatment of a subject with an agent which modulates 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 activity (*e.g.*, an agonist, antagonist,
20 peptidomimetic, protein, peptide, nucleic acid, or small molecule identified by the screening assays described herein) including the steps of (i) obtaining a pre-administration sample from a subject prior to administration of the agent; (ii) detecting the level of expression of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein, mRNA, or
25 genomic DNA in the pre-administration sample; (iii) obtaining one or more post-administration samples from the subject; (iv) detecting the level of expression or activity of the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein, mRNA, or genomic DNA in the post-administration samples; (v) comparing the level of expression or activity
30 of the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein, mRNA, or genomic DNA in the pre-administration sample with the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein, mRNA, or genomic DNA in the post administration

sample or samples; and (vi) altering the administration of the agent to the subject accordingly. For example, increased administration of the agent may be desirable to increase the expression or activity of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 to higher levels than detected, *i.e.*, to increase the effectiveness of the agent. Alternatively, decreased administration of the agent may be desirable to decrease expression or activity of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 to lower levels than detected, *i.e.* to decrease the effectiveness of the agent. According to such an embodiment, 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 expression or activity may be used as an indicator of the effectiveness of an agent, even in the absence of an observable phenotypic response.

Methods of Treatment:

[00146] The present invention provides for both prophylactic and therapeutic methods of treating a subject, *e.g.*, a human, at risk of (or susceptible to) a disease. With regard to both prophylactic and therapeutic methods of treatment, such treatments may be specifically tailored or modified, based on knowledge obtained from the field of pharmacogenomics. "Pharmacogenomics," as used herein, refers to the application of genomics technologies such as gene sequencing, statistical genetics, and gene expression analysis to drugs in clinical development and on the market. More specifically, the term refers to the study of how a patient's genes determine his or her response to a drug (*e.g.*, a patient's "drug response phenotype", or "drug response genotype").

[00147] Thus, another aspect of the invention provides methods for tailoring an subject's prophylactic or therapeutic treatment with either the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 molecules of the present invention or 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 modulators according to that individual's drug response genotype. Pharmacogenomics allows a clinician or physician to target prophylactic or therapeutic treatments to patients who will most benefit from the treatment and to avoid treatment of patients who will experience toxic drug-related side effects.

Prophylactic Methods

[00148] In one aspect, the invention provides a method for preventing in a subject, a disease by administering to the subject an agent which modulates 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 expression or 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 activity. Subjects at risk for a urological disorder, *e.g.*, BPH and/or UI, can be identified by, for example, any or a combination of the diagnostic or prognostic assays described herein. Administration of a prophylactic agent can occur prior to the manifestation of symptoms characteristic of aberrant 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 expression or activity, such that a disease is prevented or, alternatively, delayed in its progression. Depending on the type of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 aberrancy, for example, a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 agonist or 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 antagonist agent can be used for treating the subject. The appropriate agent can be determined based on screening assays described herein.

Therapeutic Methods

[00149] Described herein are methods and compositions whereby a urological disorder may be ameliorated. Certain urological disorders are brought about, at least in part, by an excessive level of a gene product, or by the presence of a gene product exhibiting an abnormal or excessive activity. As such, the reduction in the level and/or activity of such gene products would bring about the amelioration of at least one symptom of a urological disorder. Techniques for the reduction of gene expression levels or the activity of a protein are discussed below.

[00150] Alternatively, certain other urological disorders are brought about, at least in part, by the absence or reduction of the level of gene expression, or a reduction in the level of a protein's activity. As such, an increase in the level of gene expression and/or the

activity of such proteins would bring about the amelioration of at least one symptom of a urological disorder.

[00151] In some cases, the up-regulation of a gene in a disease state reflects a protective role for that gene product in responding to the disease condition. Enhancement
5 of such a gene's expression, or the activity of the gene product, will reinforce the protective effect it exerts. Some urological disease states may result from an abnormally low level of activity of such a protective gene. In these cases also, an increase in the level of gene expression and/or the activity of such gene products would bring about the amelioration of a least one symptom of a urological disorder. Techniques for increasing target gene
10 expression levels or target gene product activity levels are discussed herein.

[00152] Accordingly, another aspect of the invention pertains to methods of modulating 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 expression or activity for therapeutic purposes. Accordingly, in an exemplary embodiment, the
15 modulatory method of the invention involves contacting a cell with a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 or agent that modulates one or more of the activities of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein activity
20 associated with the cell (*e.g.*, an endothelial cell, ovarian cell, bladder cell and prostate cell). An agent that modulates 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein activity can be an agent as described herein, such as a nucleic acid or a protein, a naturally-occurring target molecule of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089,
25 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein (*e.g.*, a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 ligand or substrate), a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 antibody, a 1435,
30 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 agonist or antagonist, a peptidomimetic of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 agonist or antagonist, or other small molecule. In one embodiment, the agent stimulates one or more

1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 activities. Examples of such stimulatory agents include active 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein and a nucleic acid molecule encoding 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 that has been introduced into the cell. In another embodiment, the agent inhibits one or more 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 activities.

Examples of such inhibitory agents include antisense 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 nucleic acid molecules, anti-1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 antibodies, and 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 inhibitors. These modulatory methods can be performed *in vitro* (e.g., by culturing the cell with the agent) or, alternatively, *in vivo* (e.g., by administering the agent to a subject). As such, the present invention provides methods of treating an individual afflicted with a disease or disorder characterized by aberrant or unwanted expression or activity of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein or nucleic acid molecule. In one embodiment, the method involves administering an agent (e.g., an agent identified by a screening assay described herein), or combination of agents that modulates (e.g., upregulates or downregulates) 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 expression or activity. In another embodiment, the method involves administering a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein or nucleic acid molecule as therapy to compensate for reduced, aberrant, or unwanted 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 expression or activity.

[00153] Stimulation of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 activity is desirable in situations in which 1435, 559, 34021, 44099, 25278, 641, 260,

55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 is abnormally downregulated and/or in which increased 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 activity is likely to have a beneficial effect.

5 Likewise, inhibition of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 activity is desirable in situations in which 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 is abnormally upregulated and/or in which decreased 1435, 559, 34021, 44099, 25278, 641, 10 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 activity is likely to have a beneficial effect.

Methods for Inhibiting Target Gene Expression, Synthesis, or Activity

[00154] As discussed above, genes involved in cardiovascular disorders may cause
15 such disorders via an increased level of gene activity. In some cases, such up-regulation may have a causative or exacerbating effect on the disease state. A variety of techniques may be used to inhibit the expression, synthesis, or activity of such genes and/or proteins.

[00155] For example, compounds such as those identified through assays described above, which exhibit inhibitory activity, may be used in accordance with the invention to
20 ameliorate at least one symptom of a urological disorder. Such molecules may include, but are not limited to, small organic molecules, peptides, antibodies, and the like.

[00156] For example, compounds can be administered that compete with endogenous ligand for the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351
25 protein. The resulting reduction in the amount of ligand-bound 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein will modulate endothelial cell physiology. Compounds that can be particularly useful for this purpose include, for example, soluble proteins or peptides, such as peptides comprising one or more of the extracellular domains,
30 or portions and/or analogs thereof, of the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein, including, for example, soluble fusion proteins such as Ig-tailed fusion proteins. (For a discussion of the production of Ig-tailed fusion proteins, see, for example, U.S. Pat. No. 5,116,964). Alternatively, compounds, such as ligand analogs or

antibodies, that bind to the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 receptor site, but do not activate the protein, (e.g., receptor-ligand antagonists) can be effective in inhibiting 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein activity.

[00157] Further, antisense and ribozyme molecules which inhibit expression of the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene may also be used in accordance with the invention to inhibit aberrant 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene activity. Still further, triple helix molecules may be utilized in inhibiting aberrant 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene activity.

[00158] The antisense nucleic acid molecules used in the methods of the invention are typically administered to a subject or generated *in situ* such that they hybridize with or bind to cellular mRNA and/or genomic DNA encoding a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein to thereby inhibit expression of the protein, e.g., by inhibiting transcription and/or translation. The hybridization can be by conventional nucleotide complementarity to form a stable duplex, or, for example, in the case of an antisense nucleic acid molecule which binds to DNA duplexes, through specific interactions in the major groove of the double helix. An example of a route of administration of antisense nucleic acid molecules of the invention include direct injection at a tissue site. Alternatively, antisense nucleic acid molecules can be modified to target selected cells and then administered systemically. For example, for systemic administration, antisense molecules can be modified such that they specifically bind to receptors or antigens expressed on a selected cell surface, e.g., by linking the antisense nucleic acid molecules to peptides or antibodies which bind to cell surface receptors or antigens. The antisense nucleic acid molecules can also be delivered to cells using the vectors described herein. To achieve sufficient intracellular concentrations of the antisense molecules, vector constructs in which the antisense nucleic acid molecule is placed under the control of a strong pol II or pol III promoter are preferred.

[00159] In yet another embodiment, an antisense nucleic acid molecule used in the methods of the invention is an α -anomeric nucleic acid molecule. An α -anomeric nucleic acid molecule forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual β -units, the strands run parallel to each other (Gaultier *et al.* (1987)

5 *Nucleic Acids. Res.* 15:6625-6641). The antisense nucleic acid molecule can also comprise a 2'-o-methylribonucleotide (Inoue *et al.* (1987) *Nucleic Acids Res.* 15:6131-6148) or a chimeric RNA-DNA analogue (Inoue *et al.* (1987) *FEBS Lett.* 215:327-330).

[00160] In still another embodiment, an antisense nucleic acid used in the methods of the invention is a ribozyme. Ribozymes are catalytic RNA molecules with ribonuclease activity which are capable of cleaving a single-stranded nucleic acid, such as an mRNA, to which they have a complementary region. Thus, ribozymes (*e.g.*, hammerhead ribozymes (described in Haselhoff and Gerlach (1988) *Nature* 334:585-591)) can be used to catalytically cleave 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 mRNA transcripts to thereby inhibit translation of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 mRNA. A ribozyme having specificity for a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351-encoding nucleic acid can be designed based upon the nucleotide sequence of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 cDNA disclosed herein (*i.e.*, SEQ ID NO:1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61 or 64). For example, a derivative of a *Tetrahymena* L-19 IVS RNA can be constructed in which the nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved in a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351-encoding mRNA (see, for example, Cech *et al.* U.S. Patent No. 4,987,071; and Cech *et al.* U.S. Patent No. 5,116,742). Alternatively, 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 mRNA can be used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules (see, for example, Bartel, D. and Szostak, J.W. (1993) *Science* 261:1411-1418).

[00161] 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene expression can

also be inhibited by targeting nucleotide sequences complementary to the regulatory region of the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 (*e.g.*, the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 promoter and/or enhancers) to form triple helical structures that prevent transcription of the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene in target cells (see, for example, Helene, C. (1991) *Anticancer Drug Des.* 6(6):569-84; Helene, C. *et al.* (1992) *Ann. N.Y. Acad. Sci.* 660:27-36; and Maher, L.J. (1992) *Bioassays* 14(12):807-15).

[00162] Antibodies that are both specific for the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein and interfere with its activity may also be used to modulate or inhibit 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein function. Such antibodies may be generated using standard techniques described herein, against the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein itself or against peptides corresponding to portions of the protein. Such antibodies include but are not limited to polyclonal, monoclonal, Fab fragments, single chain antibodies, or chimeric antibodies.

[00163] In instances where the target gene protein is intracellular and whole antibodies are used, internalizing antibodies may be preferred. Lipofectin liposomes may be used to deliver the antibody or a fragment of the Fab region which binds to the target epitope into cells. Where fragments of the antibody are used, the smallest inhibitory

[00164] fragment which binds to the target protein's binding domain is preferred. For example, peptides having an amino acid sequence corresponding to the domain of the variable region of the antibody that binds to the target gene protein may be used. Such peptides may be synthesized chemically or produced via recombinant DNA technology using

[00165] methods well known in the art (described in, for example, Creighton (1983), *supra*; and Sambrook *et al.* (1989) *supra*). Single chain neutralizing antibodies which bind to intracellular target gene epitopes may also be administered. Such single chain antibodies may be administered, for example, by expressing nucleotide sequences encoding single-

chain antibodies within the target cell population by utilizing, for example, techniques such as those described in Marasco *et al.* (1993) *Proc. Natl. Acad. Sci. USA* 90:7889-7893).

[00166] In some instances, the target gene protein is extracellular, or is a transmembrane protein, such as the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein. Antibodies that are specific for one or more extracellular domains of the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein, for example, and that interfere with its activity, are particularly useful in treating urological disorder or a urological disorder. Such antibodies are especially efficient because they can access the target domains directly from the bloodstream. Any of the administration techniques described below which are appropriate for peptide administration may be utilized to effectively administer inhibitory target gene antibodies to their site of action.

15 Methods for Restoring or Enhancing Target Gene Activity

[00167] Genes that cause a urological disorder may be underexpressed within BPH and/or UI. Alternatively, the activity of the protein products of such genes may be decreased, leading to the development of urological disorder. Such down-regulation of gene expression or decrease of protein activity might have a causative or exacerbating effect on the disease state.

[00168] In some cases, genes that are up-regulated in the disease state might be exerting a protective effect. A variety of techniques may be used to increase the expression, synthesis, or activity of genes and/or proteins that exert a protective effect in response to a urological disorder.

25 [00169] Described in this section are methods whereby the level of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 activity may be increased to levels wherein the symptoms of the urological disorder are ameliorated. The level of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 activity may be increased, for example, by either increasing the level of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene expression or by increasing the level of active 1435, 559, 34021, 44099, 25278, 641, 260,

55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein which is present.

[00170] For example, a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein, at a level sufficient to ameliorate at least one symptom of a urological disorder may be administered to a patient exhibiting such symptoms. Any of the techniques discussed below may be used for such administration. One of skill in the art will readily know how to determine the concentration of effective, non-toxic doses of the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein, utilizing techniques such as those described below.

[00171] Additionally, RNA sequences encoding a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein may be directly administered to a patient exhibiting a urological disorder, at a concentration sufficient to produce a level of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein such that a urological disorder are ameliorated. Any of the techniques discussed below, which achieve intracellular administration of compounds, such as, for example, liposome administration, may be used for the administration of such RNA molecules. The RNA molecules may be produced, for example, by recombinant techniques such as those described herein.

[00172] Further, subjects may be treated by gene replacement therapy. One or more copies of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene, or a portion thereof, that directs the production of a normal 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein with 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 function, may be inserted into cells using vectors which include, but are not limited to adenovirus, adeno-associated virus, and retrovirus vectors, in addition to other particles that introduce DNA into cells, such as liposomes. Additionally, techniques such as those described above may be used for the introduction of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene sequences into human cells.

[00173] Cells, preferably, autologous cells, containing 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 expressing gene sequences may then be introduced or reintroduced into the subject at positions which allow for the amelioration of at least one
5 symptom of a urological disorder. Such cell replacement techniques may be preferred, for example, when the gene product is a secreted, extracellular gene product.

Pharmaceutical Compositions

[00174] Another aspect of the invention pertains to methods for treating a subject
10 suffering from a disease. These methods involve administering to a subject an agent which modulates 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 expression or activity (*e.g.*, an agent identified by a screening assay described herein), or a combination of such agents. In another embodiment, the method involves administering to a subject a 1435, 559, 34021,
15 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein or nucleic acid molecule as therapy to compensate for reduced, aberrant, or unwanted 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 expression or activity.

[00175] Stimulation of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351
20 activity is desirable in situations in which 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 is abnormally downregulated and/or in which increased 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985,
25 13237, 13601, 18926, 318, 2058 or 6351 activity is likely to have a beneficial effect. Likewise, inhibition of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 activity is desirable in situations in which 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 is
30 abnormally upregulated and/or in which decreased 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 activity is likely to have a beneficial effect.

[00176] The agents which modulate 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 activity can be administered to a subject using pharmaceutical compositions suitable for such administration. Such compositions typically comprise the agent (*e.g.*,
5 nucleic acid molecule, protein, or antibody) and a pharmaceutically acceptable carrier. As used herein the language "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible
10 with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

[00177] A pharmaceutical composition used in the therapeutic methods of the invention is formulated to be compatible with its intended route of administration.
15 Examples of routes of administration include parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, inhalation), transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or
20 other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation
25 can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[00178] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous
30 administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, NJ) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and

fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, and sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[00179] Sterile injectable solutions can be prepared by incorporating the agent that modulates 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 activity (*e.g.*, a fragment of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein or an anti-1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 antibody) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[00180] Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the

following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange
5 flavoring.

[00181] For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

10 [00182] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of
15 nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

[00183] The agents that modulate 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 activity can also be prepared in the form of suppositories (*e.g.*, with conventional
20 suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

[00184] In one embodiment, the agents that modulate 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 activity are prepared with carriers that will protect the
25 compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be
30 obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811.

[00185] It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to
5 produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the agent that modulates 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 activity and the particular therapeutic effect
10 to be achieved, and the limitations inherent in the art of compounding such an agent for the treatment of subjects.

[00186] Toxicity and therapeutic efficacy of such agents can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose
15 therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and can be expressed as the ratio LD50/ED50. Agents which exhibit large therapeutic indices are preferred. While agents that exhibit toxic side effects may be used, care should be taken to design a delivery system that targets such agents to the site of affected tissue in order to minimize potential damage to
20 uninfected cells and, thereby, reduce side effects.

[00187] The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 modulating agents lies preferably within a
25 range of circulating concentrations that include the ED50 with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any agent used in the therapeutic methods of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma
30 concentration range that includes the IC50 (*i.e.*, the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography.

[00188] As defined herein, a therapeutically effective amount of protein or polypeptide (*i.e.*, an effective dosage) ranges from about 0.001 to 30 mg/kg body weight, preferably about 0.01 to 25 mg/kg body weight, more preferably about 0.1 to 20 mg/kg body weight, and even more preferably about 1 to 10 mg/kg, 2 to 9 mg/kg, 3 to 8 mg/kg, 4 to 7 mg/kg, or 5 to 6 mg/kg body weight. The skilled artisan will appreciate that certain factors may influence the dosage required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of a protein, polypeptide, or antibody can include a single treatment or, preferably, can include a series of treatments.

[00189] In a preferred example, a subject is treated with antibody, protein, or polypeptide in the range of between about 0.1 to 20 mg/kg body weight, one time per week for between about 1 to 10 weeks, preferably between 2 to 8 weeks, more preferably between about 3 to 7 weeks, and even more preferably for about 4, 5, or 6 weeks. It will also be appreciated that the effective dosage of antibody, protein, or polypeptide used for treatment may increase or decrease over the course of a particular treatment. Changes in dosage may result and become apparent from the results of diagnostic assays as described herein.

[00190] The present invention encompasses agents which modulate expression or activity. An agent may, for example, be a small molecule. For example, such small molecules include, but are not limited to, peptides, peptidomimetics, amino acids, amino acid analogs, polynucleotides, polynucleotide analogs, nucleotides, nucleotide analogs, organic or inorganic compounds (*i.e.*, including heteroorganic and organometallic compounds) having a molecular weight less than about 10,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 5,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 1,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 500 grams per mole, and salts, esters, and other pharmaceutically acceptable forms of such compounds. It is understood that appropriate doses of small molecule agents depends upon a number of factors within the ken of the ordinarily skilled physician, veterinarian, or researcher. The dose(s) of the small molecule will vary, for example, depending upon the identity, size, and condition of the subject or sample being treated, further depending upon the route by which the composition is to be administered, if applicable, and the effect

which the practitioner desires the small molecule to have upon the nucleic acid or polypeptide of the invention.

[00191] Exemplary doses include milligram or microgram amounts of the small molecule per kilogram of subject or sample weight (*e.g.*, about 1 microgram per kilogram to about 500 milligrams per kilogram, about 100 micrograms per kilogram to about 5 milligrams per kilogram, or about 1 microgram per kilogram to about 50 micrograms per kilogram). It is

[00192] furthermore understood that appropriate doses of a small molecule depend upon the potency of the small molecule with respect to the expression or activity to be modulated. Such appropriate doses may be determined using the assays described herein. When one or more of these small molecules is to be administered to an animal (*e.g.*, a human) in order to modulate expression or activity of a polypeptide or nucleic acid of the invention, a physician, veterinarian, or researcher may, for example, prescribe a relatively low dose at first, subsequently increasing the dose until an appropriate response is obtained. In addition, it is understood that the specific dose level for any particular animal subject will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, gender, and diet of the subject, the time of administration, the route of administration, the rate of excretion, any drug combination, and the degree of expression or activity to be modulated.

[00193] Further, an antibody (or fragment thereof) may be conjugated to a therapeutic moiety such as a cytotoxin, a therapeutic agent or a radioactive metal ion. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include taxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (*e.g.*, methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (*e.g.*, mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (*e.g.*, daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (*e.g.*, dactinomycin (formerly actinomycin), bleomycin,

mithramycin, and anthramycin (AMC)), and anti-mitotic agents (*e.g.*, vincristine and vinblastine).

[00194] The conjugates of the invention can be used for modifying a given biological response, the drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide
5 possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, alpha-interferon, beta-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator; or biological response modifiers such as, for
10 example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophase colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

[00195] Techniques for conjugating such therapeutic moiety to antibodies are well known, see, *e.g.*, Armon *et al.*, "Monoclonal Antibodies For Immunotargeting Of Drugs In
15 Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld *et al.* (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom *et al.*, "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson *et al.* (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies '84: Biological And Clinical Applications, Pinchera *et al.* (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The
20 Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin *et al.* (eds.), pp. 303-16 (Academic Press 1985), and Thorpe *et al.*, "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", Immunol. Rev., 62:119-58 (1982). Alternatively, an antibody can be
25 conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980.

[00196] The nucleic acid molecules used in the methods of the invention can be inserted into vectors and used as gene therapy vectors. Gene therapy vectors can be delivered to a subject by, for example, intravenous injection, local administration (see U.S.
30 Patent 5,328,470) or by stereotactic injection (see, *e.g.*, Chen *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91:3054-3057). The pharmaceutical preparation of the gene therapy vector can include the gene therapy vector in an acceptable diluent, or can comprise a slow release matrix in which the gene delivery vehicle is imbedded. Alternatively, where the complete gene delivery vector can be produced intact from recombinant cells, *e.g.*, retroviral vectors,

the pharmaceutical preparation can include one or more cells which produce the gene delivery system.

Pharmacogenomics

5 [00197] In conjunction with the therapeutic methods of the invention, pharmacogenomics (*i.e.*, the study of the relationship between a subject's genotype and that subject's response to a foreign compound or drug) may be considered. Differences in metabolism of therapeutics can lead to severe toxicity or therapeutic failure by altering the relation between dose and blood concentration of the pharmacologically active drug. Thus, 10 a physician or clinician may consider applying knowledge obtained in relevant pharmacogenomics studies in determining whether to administer an agent which modulates 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 activity, as well as tailoring the dosage and/or therapeutic regimen of treatment with an agent which modulates 1435, 559, 15 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 activity.

[00198] Pharmacogenomics deals with clinically significant hereditary variations in the response to drugs due to altered drug disposition and abnormal action in affected persons. See, for example, Eichelbaum, M. *et al.* (1996) *Clin. Exp. Pharmacol. Physiol.* 20 23(10-11): 983-985 and Linder, M.W. *et al.* (1997) *Clin. Chem.* 43(2):254-266. In general, two types of pharmacogenetic conditions can be differentiated. Genetic conditions transmitted as a single factor altering the way drugs act on the body (altered drug action) or genetic conditions transmitted as single factors altering the way the body acts on drugs (altered drug metabolism). These pharmacogenetic conditions can occur either as rare 25 genetic defects or as naturally-occurring polymorphisms. For example, glucose-6-phosphate aminopeptidase deficiency (G6PD) is a common inherited enzymopathy in which the main clinical complication is haemolysis after ingestion of oxidant drugs (anti-malarials, sulfonamides, analgesics, nitrofurans) and consumption of fava beans.

[00199] One pharmacogenomics approach to identifying genes that predict drug 30 response, known as "a genome-wide association", relies primarily on a high-resolution map of the human genome consisting of already known gene-related markers (*e.g.*, a "bi-allelic" gene marker map which consists of 60,000-100,000 polymorphic or variable sites on the human genome, each of which has two variants). Such a high-resolution genetic map can be compared to a map of the genome of each of a statistically significant number of

patients taking part in a Phase II/III drug trial to identify markers associated with a particular observed drug response or side effect. Alternatively, such a high resolution map can be generated from a combination of some ten million known single nucleotide polymorphisms (SNPs) in the human genome. As used herein, a "SNP" is a common alteration that occurs in a single nucleotide base in a stretch of DNA. For example, a SNP may occur once per every 1000 bases of DNA. A SNP may be involved in a disease process, however, the vast majority may not be disease-associated. Given a genetic map based on the occurrence of such SNPs, individuals can be grouped into genetic categories depending on a particular pattern of SNPs in their individual genome. In such a manner, treatment regimens can be tailored to groups of genetically similar individuals, taking into account traits that may be common among such genetically similar individuals.

[00200] Alternatively, a method termed the "candidate gene approach" can be utilized to identify genes that predict drug response. According to this method, if a gene that encodes a drug target is known (*e.g.*, a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein used in the methods of the present invention), all common variants of that gene can be fairly easily identified in the population and it can be determined if having one version of the gene versus another is associated with a particular drug response.

[00201] As an illustrative embodiment, the activity of drug metabolizing enzymes is a major determinant of both the intensity and duration of drug action. The discovery of genetic polymorphisms of drug metabolizing enzymes (*e.g.*, N-acetyltransferase 2 (NAT 2) and the cytochrome P450 enzymes CYP2D6 and CYP2C19) has provided an explanation as to why some patients do not obtain the expected drug effects or show exaggerated drug response and serious toxicity after taking the standard and safe dose of a drug. These polymorphisms are expressed in two phenotypes in the population, the extensive metabolizer (EM) and poor metabolizer (PM). The prevalence of PM is different among different populations. For example, the gene coding for CYP2D6 is highly polymorphic and several mutations have been identified in PM, which all lead to the absence of functional CYP2D6. Poor metabolizers of CYP2D6 and CYP2C19 quite frequently experience exaggerated drug response and side effects when they receive standard doses. If a metabolite is the active therapeutic moiety, PM show no therapeutic response, as demonstrated for the analgesic effect of codeine mediated by its CYP2D6-formed metabolite morphine. The other extreme are the so called ultra-rapid metabolizers who do

not respond to standard doses. Recently, the molecular basis of ultra-rapid metabolism has been identified to be due to CYP2D6 gene amplification.

[00202] Alternatively, a method termed the "gene expression profiling" can be utilized to identify genes that predict drug response. For example, the gene expression of
5 an animal dosed with a drug (*e.g.*, a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 molecule or 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 modulator used in the methods of the present invention) can give an indication whether gene pathways related
10 to toxicity have been turned on.

[00203] Information generated from more than one of the above pharmacogenomics approaches can be used to determine appropriate dosage and treatment regimens for prophylactic or therapeutic treatment of a subject. This knowledge, when applied to dosing or drug selection, can avoid adverse reactions or therapeutic failure and, thus, enhance
15 therapeutic or prophylactic efficiency when treating a subject suffering from a cardiovascular disease, *e.g.*, atherosclerosis, with an agent which modulates 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 activity.

20 Recombinant Expression Vectors and Host Cells Used in the Methods of the Invention

[00204] The methods of the invention (*e.g.*, the screening assays described herein) include the use of vectors, preferably expression vectors, containing a nucleic acid encoding a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein (or a portion
25 thereof). As used herein, the term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments can be ligated. Another type of vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome. Certain vectors are capable of autonomous
30 replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they

are operatively linked. Such vectors are referred to herein as "expression vectors". In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, "plasmid" and "vector" can be used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors, such as viral vectors (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

[00205] The recombinant expression vectors to be used in the methods of the invention comprise a nucleic acid of the invention in a form suitable for expression of the nucleic acid in a host cell, which means that the recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression, which is operatively linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, "operably linked" is intended to mean that the nucleotide sequence of interest is linked to the regulatory sequence(s) in a manner which allows for expression of the nucleotide sequence (*e.g.*, in an *in vitro* transcription/translation system or in a host cell when the vector is introduced into the host cell). The term "regulatory sequence" is intended to include promoters, enhancers and other expression control elements (*e.g.*, polyadenylation signals). Such regulatory sequences are described, for example, in Goeddel (1990) *Methods Enzymol.* 185:3-7. Regulatory sequences include those which direct constitutive expression of a nucleotide sequence in many types of host cells and those which direct expression of the nucleotide sequence only in certain host cells (*e.g.*, tissue-specific regulatory sequences). It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, and the like. The expression vectors of the invention can be introduced into host cells to thereby produce proteins or peptides, including fusion proteins or peptides, encoded by nucleic acids as described herein (*e.g.*, 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 proteins, mutant forms of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 proteins, fusion proteins, and the like).

[00206] The recombinant expression vectors to be used in the methods of the invention can be designed for expression of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318,

2058 or 6351 proteins in prokaryotic or eukaryotic cells. For example, 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 proteins can be expressed in bacterial cells such as *E. coli*, insect cells (using baculovirus expression vectors), yeast cells, or mammalian
5 cells. Suitable host cells are discussed further in Goeddel (1990) *supra*. Alternatively, the recombinant expression vector can be transcribed and translated *in vitro*, for example using T7 promoter regulatory sequences and T7 polymerase.

[00207] Expression of proteins in prokaryotes is most often carried out in *E. coli* with vectors containing constitutive or inducible promoters directing the expression of
10 either fusion or non-fusion proteins. Fusion vectors add a number of amino acids to a protein encoded therein, usually to the amino terminus of the recombinant protein. Such fusion vectors typically serve three purposes: 1) to increase expression of recombinant protein; 2) to increase the solubility of the recombinant protein; and 3) to aid in the purification of the recombinant protein by acting as a ligand in affinity purification. Often,
15 in fusion expression vectors, a proteolytic cleavage site is introduced at the junction of the fusion moiety and the recombinant protein to enable separation of the recombinant protein from the fusion moiety subsequent to purification of the fusion protein. Such enzymes, and their cognate recognition sequences, include Factor Xa, thrombin and enterokinase.

Typical fusion expression vectors include pGEX (Pharmacia Biotech Inc; Smith, D.B. and
20 Johnson, K.S. (1988) *Gene* 67:31-40), pMAL (New England Biolabs, Beverly, MA) and pRIT5 (Pharmacia, Piscataway, NJ) which fuse glutathione S-transferase (GST), maltose E binding protein, or protein A, respectively, to the target recombinant protein.

[00208] Purified fusion proteins can be utilized in 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601,
25 18926, 318, 2058 or 6351 activity assays, (*e.g.*, direct assays or competitive assays described in detail below), or to generate antibodies specific for 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 proteins. In a preferred embodiment, a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985,
30 13237, 13601, 18926, 318, 2058 or 6351 fusion protein expressed in a retroviral expression vector of the present invention can be utilized to infect bone marrow cells which are subsequently transplanted into irradiated recipients. The pathology of the subject recipient is then examined after sufficient time has passed (*e.g.*, six weeks).

[00209] In another embodiment, a nucleic acid of the invention is expressed in mammalian cells using a mammalian expression vector. Examples of mammalian expression vectors include pCDM8 (Seed, B. (1987) *Nature* 329:840) and pMT2PC (Kaufman *et al.* (1987) *EMBO J.* 6:187-195). When used in mammalian cells, the expression vector's control functions are often provided by viral regulatory elements. For example, commonly used promoters are derived from polyoma, Adenovirus 2, cytomegalovirus and Simian Virus 40. For other suitable expression systems for both prokaryotic and eukaryotic cells see chapters 16 and 17 of Sambrook, J. *et al.*, *Molecular Cloning: A Laboratory Manual*. 2nd ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989.

[00210] In another embodiment, the recombinant mammalian expression vector is capable of directing expression of the nucleic acid preferentially in a particular cell type (*e.g.*, tissue-specific regulatory elements are used to express the nucleic acid).

[00211] The methods of the invention may further use a recombinant expression vector comprising a DNA molecule of the invention cloned into the expression vector in an antisense orientation. That is, the DNA molecule is operatively linked to a regulatory sequence in a manner which allows for expression (by transcription of the DNA molecule) of an RNA molecule which is antisense to 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 mRNA. Regulatory sequences operatively linked to a nucleic acid cloned in the antisense orientation can be chosen which direct the continuous expression of the antisense RNA molecule in a variety of cell types, for instance viral promoters and/or enhancers, or regulatory sequences can be chosen which direct constitutive, tissue specific, or cell type specific expression of antisense RNA. The antisense expression vector can be in the form of a recombinant plasmid, phagemid, or attenuated virus in which antisense nucleic acids are produced under the control of a high efficiency regulatory region, the activity of which can be determined by the cell type into which the vector is introduced. For a discussion of the regulation of gene expression using antisense genes, see Weintraub, H. *et al.*, Antisense RNA as a molecular tool for genetic analysis, *Reviews - Trends in Genetics*, Vol. 1(1) 1986.

[00212] Another aspect of the invention pertains to the use of host cells into which a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 nucleic acid molecule of the invention is introduced, *e.g.*, a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407,

42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 nucleic acid molecule within a recombinant expression vector or a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 nucleic acid molecule containing sequences
5 which allow it to homologously recombine into a specific site of the host cell's genome. The terms "host cell" and "recombinant host cell" are used interchangeably herein. It is understood that such terms refer not only to the particular subject cell but to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in
10 fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

[00213] A host cell can be any prokaryotic or eukaryotic cell. For example, a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein can be expressed in bacterial
15 cells such as *E. coli*, insect cells, yeast or mammalian cells (such as Chinese hamster ovary cells (CHO) or COS cells). Other suitable host cells are known to those skilled in the art.

[00214] Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. As used herein, the terms "transformation" and "transfection" are intended to refer to a variety of art-recognized
20 techniques for introducing foreign nucleic acid (*e.g.*, DNA) into a host cell, including calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, or electroporation. Suitable methods for transforming or transfecting host cells can be found in Sambrook *et al.* (*Molecular Cloning: A Laboratory Manual*, 2nd, ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press,
25 Cold Spring Harbor, NY, 1989), and other laboratory manuals.

[00215] A host cell used in the methods of the invention, such as a prokaryotic or eukaryotic host cell in culture, can be used to produce (*i.e.*, express) a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein. Accordingly, the invention further
30 provides methods for producing a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein using the host cells of the invention. In one embodiment, the method comprises culturing the host cell of the invention (into which a recombinant expression vector encoding a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656,

62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein has been introduced) in a suitable medium such that a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein is produced. In another embodiment, the method further comprises
5 isolating a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein from the medium or the host cell.

Isolated Nucleic Acid Molecules Used in the Methods of the Invention

10 [00216] The methods of the invention include the use of isolated nucleic acid molecules that encode 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 proteins or biologically active portions thereof, as well as nucleic acid fragments sufficient for use as hybridization probes to identify 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407,
15 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 - encoding nucleic acid molecules (e.g., 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 mRNA) and fragments for use as PCR primers for the amplification or mutation of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323,
20 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 nucleic acid molecules. As used herein, the term "nucleic acid molecule" is intended to include DNA molecules (e.g., cDNA or genomic DNA) and RNA molecules (e.g., mRNA) and analogs of the DNA or RNA generated using nucleotide analogs. The nucleic acid molecule can be single-stranded or double-stranded, but preferably is double-stranded DNA.

25 [00217] A nucleic acid molecule used in the methods of the present invention, e.g., a nucleic acid molecule having the nucleotide sequence of SEQ ID NO:1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61 or 64, or a portion thereof, can be isolated using standard molecular biology techniques and the sequence information provided herein. Using all or portion of the nucleic acid sequence of SEQ ID NO:1, 4, 7,
30 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61 or 64, as a hybridization probe, 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 nucleic acid molecules can be isolated using standard hybridization and cloning techniques (e.g., as described in Sambrook, J., Fritsh, E. F., and Maniatis, T. *Molecular Cloning: A Laboratory Manual*.

2nd, ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989).

[00218] Moreover, a nucleic acid molecule encompassing all or a portion of SEQ ID NO:1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61 or 64 can be isolated by the polymerase chain reaction (PCR) using synthetic oligonucleotide primers designed based upon the sequence of SEQ ID NO:1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61 or 64.

[00219] A nucleic acid used in the methods of the invention can be amplified using cDNA, mRNA or, alternatively, genomic DNA as a template and appropriate oligonucleotide primers according to standard PCR amplification techniques. Furthermore, oligonucleotides corresponding to 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 nucleotide sequences can be prepared by standard synthetic techniques, e.g., using an automated DNA synthesizer.

[00220] In a preferred embodiment, the isolated nucleic acid molecules used in the methods of the invention comprise the nucleotide sequence shown in SEQ ID NO:1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61 or 64, a complement of the nucleotide sequence shown in SEQ ID NO:1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61 or 64, or a portion of any of these nucleotide sequences. A nucleic acid molecule which is complementary to the nucleotide sequence shown in SEQ ID NO:1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61 or 64, is one which is sufficiently complementary to the nucleotide sequence shown in SEQ ID NO:1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61 or 64 such that it can hybridize to the nucleotide sequence shown in SEQ ID NO:1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61 or 64 thereby forming a stable duplex.

[00221] In still another preferred embodiment, an isolated nucleic acid molecule used in the methods of the present invention comprises a nucleotide sequence which is at least about 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more identical to the entire length of the nucleotide sequence shown in SEQ ID NO:1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61 or 64, or a portion of any of this nucleotide sequence.

[00222] Moreover, the nucleic acid molecules used in the methods of the invention can comprise only a portion of the nucleic acid sequence of SEQ ID NO:1, 4, 7, 10, 13, 16,

19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61 or 64, for example, a fragment which can be used as a probe or primer or a fragment encoding a portion of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein, *e.g.*, a biologically active portion of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein. The probe/primer typically comprises substantially purified oligonucleotide. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 12 or 15, preferably about 20 or 25, more preferably about 30, 35, 40, 45, 50, 55, 60, 65, or 75 consecutive nucleotides of a sense sequence of SEQ ID NO:1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61 or 64, of an anti-sense sequence of SEQ ID NO:1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61 or 64, or of a naturally occurring allelic variant or mutant of SEQ ID NO:1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61 or 64. In one embodiment, a nucleic acid molecule used in the methods of the present invention comprises a nucleotide sequence which is greater than 100, 100-200, 200-300, 300-400, 400-500, 500-600, 600-700, 700-800, 800-900, 900-1000, 1000-1100, 1100-1200, 1200-1300, or more nucleotides in length and hybridizes under stringent hybridization conditions to a nucleic acid molecule of SEQ ID NO:1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61 or 64.

[00223] As used herein, the term "hybridizes under stringent conditions" is intended to describe conditions for hybridization and washing under which nucleotide sequences that are significantly identical or homologous to each other remain hybridized to each other. Preferably, the conditions are such that sequences at least about 70%, more preferably at least about 80%, even more preferably at least about 85% or 90% identical to each other remain hybridized to each other. Such stringent conditions are known to those skilled in the art and can be found in *Current Protocols in Molecular Biology*, Ausubel *et al.*, eds., John Wiley & Sons, Inc. (1995), sections 2, 4 and 6. Additional stringent conditions can be found in *Molecular Cloning: A Laboratory Manual*, Sambrook *et al.*, Cold Spring Harbor Press, Cold Spring Harbor, NY (1989), chapters 7, 9 and 11. A preferred, non-limiting example of stringent hybridization conditions includes hybridization in 4X sodium chloride/sodium citrate (SSC), at about 65-70°C (or hybridization in 4X SSC plus 50% formamide at about 42-50°C) followed by one or more washes in 1X SSC, at about 65-70°C. A preferred, non-limiting example of highly

stringent hybridization conditions includes hybridization in 1X SSC, at about 65-70°C (or hybridization in 1X SSC plus 50% formamide at about 42-50°C) followed by one or more washes in 0.3X SSC, at about 65-70°C. A preferred, non-limiting example of reduced stringency hybridization conditions includes hybridization in 4X SSC, at about 50-60°C (or
5 alternatively hybridization in 6X SSC plus 50% formamide at about 40-45°C) followed by one or more washes in 2X SSC, at about 50-60°C. Ranges intermediate to the above-recited values, *e.g.*, at 65-70°C or at 42-50°C are also intended to be encompassed by the present invention. SSPE (1xSSPE is 0.15M NaCl, 10mM NaH₂PO₄, and 1.25mM EDTA, pH 7.4) can be substituted for SSC (1xSSC is 0.15M NaCl and 15mM sodium citrate) in
10 the hybridization and wash buffers; washes are performed for 15 minutes each after hybridization is complete. The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10°C less than the melting temperature (T_m) of the hybrid, where T_m is determined according to the following equations. For hybrids less than 18 base pairs in length, $T_m(^{\circ}\text{C}) = 2(\# \text{ of A + T bases}) + 4(\# \text{ of G + C bases})$. For hybrids
15 between 18 and 49 base pairs in length, $T_m(^{\circ}\text{C}) = 81.5 + 16.6(\log_{10}[\text{Na}^+]) + 0.41(\% \text{G+C}) - (600/N)$, where N is the number of bases in the hybrid, and $[\text{Na}^+]$ is the concentration of sodium ions in the hybridization buffer ($[\text{Na}^+]$ for 1xSSC = 0.165 M). It will also be recognized by the skilled practitioner that additional reagents may be added to hybridization and/or wash buffers to decrease non-specific hybridization of nucleic acid
20 molecules to membranes, for example, nitrocellulose or nylon membranes, including but not limited to blocking agents (*e.g.*, BSA or salmon or herring sperm carrier DNA), detergents (*e.g.*, SDS), chelating agents (*e.g.*, EDTA), Ficoll, PVP and the like. When using nylon membranes, in particular, an additional preferred, non-limiting example of stringent hybridization conditions is hybridization in 0.25-0.5M NaH₂PO₄, 7% SDS at
25 about 65°C, followed by one or more washes at 0.02M NaH₂PO₄, 1% SDS at 65°C, see *e.g.*, Church and Gilbert (1984) *Proc. Natl. Acad. Sci. USA* 81:1991-1995, (or alternatively 0.2X SSC, 1% SDS).

[00224] In preferred embodiments, the probe further comprises a label group attached thereto, *e.g.*, the label group can be a radioisotope, a fluorescent compound, an
30 enzyme, or an enzyme co-factor. Such probes can be used as a part of a diagnostic test kit for identifying cells or tissue which misexpress a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein, such as by measuring a level of a 1435, 559, 34021, 44099,

25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 -encoding nucleic acid in a sample of cells from a subject *e.g.*, detecting 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 mRNA levels or
5 determining whether a genomic 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene has been mutated or deleted.

[00225] The methods of the invention further encompass the use of nucleic acid molecules that differ from the nucleotide sequence shown in SEQ ID NO:1, 4, 7, 10, 13,
10 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61 or 64, due to degeneracy of the genetic code and thus encode the same 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 proteins as those encoded by the nucleotide sequence shown in SEQ ID NO:1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61 or 64. In another
15 embodiment, an isolated nucleic acid molecule included in the methods of the invention has a nucleotide sequence encoding a protein having an amino acid sequence shown in SEQ ID NO:2, 5, 8, 11, 14, 17, 20, 23, 26, 29, 32, 35, 38, 41, 44, 47, 50, 53, 56, 59, 62 or 65.

[00226] The methods of the invention further include the use of allelic variants of
20 human 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351, *e.g.*, functional and non-functional allelic variants. Functional allelic variants are naturally occurring amino acid sequence variants of the human 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351
25 protein that maintain a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 activity. Functional allelic variants will typically contain only conservative substitution of one or more amino acids of SEQ ID NO:2, 5, 8, 11, 14, 17, 20, 23, 26, 29, 32, 35, 38, 41, 44, 47, 50, 53, 56, 59, 62 or 65, or substitution, deletion or insertion of non-critical residues in non-
30 critical regions of the protein.

[00227] Non-functional allelic variants are naturally occurring amino acid sequence variants of the human 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein that do not have a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656,

62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 activity. Non-functional allelic variants will typically contain a non-conservative substitution, deletion, or insertion or premature truncation of the amino acid sequence of SEQ ID NO:2, 5, 8, 11, 14, 17, 20, 23, 26, 29, 32, 35, 38, 41, 44, 47, 50, 53, 56, 59, 62 or 65, or a substitution, insertion or deletion in critical residues or critical regions of the protein.

[00228] The methods of the present invention may further use non-human orthologues of the human 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein. Orthologues of the human 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein are proteins that are isolated from non-human organisms and possess the same 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 activity.

[00229] The methods of the present invention further include the use of nucleic acid molecules comprising the nucleotide sequence of SEQ ID NO:1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61 or 64 or a portion thereof, in which a mutation has been introduced. The mutation may lead to amino acid substitutions at "non-essential" amino acid residues or at "essential" amino acid residues. A "non-essential" amino acid residue is a residue that can be altered from the wild-type sequence of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 (*e.g.*, the sequence of SEQ ID NO:2, 5, 8, 11, 14, 17, 20, 23, 26, 29, 32, 35, 38, 41, 44, 47, 50, 53, 56, 59, 62 or 65) without altering the biological activity, whereas an "essential" amino acid residue is required for biological activity. For example, amino acid residues that are conserved among the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 proteins of the present invention are not likely to be amenable to alteration.

[00230] Mutations can be introduced into SEQ ID NO:1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61 or 64, by standard techniques, such as site-directed mutagenesis and PCR-mediated mutagenesis. Preferably, conservative amino acid substitutions are made at one or more predicted non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids

with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, glycine, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains
5 (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Thus, a predicted nonessential amino acid residue in a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein is preferably replaced with another amino acid residue from the same side chain family. Alternatively, in another embodiment,
10 mutations can be introduced randomly along all or part of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318,
15 2058 or 6351 biological activity to identify mutants that retain activity. Following mutagenesis of SEQ ID NO:1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61 or 64, the encoded protein can be expressed recombinantly and the activity of the protein can be determined using the assay described herein.

[00231] Another aspect of the invention pertains to the use of isolated nucleic acid
20 molecules which are antisense to the nucleotide sequence of SEQ ID NO:1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61 or 64. An "antisense" nucleic acid comprises a nucleotide sequence which is complementary to a "sense" nucleic acid encoding a protein, *e.g.*, complementary to the coding strand of a double-stranded cDNA molecule or complementary to an mRNA sequence. Accordingly, an antisense nucleic acid
25 can hydrogen bond to a sense nucleic acid. The antisense nucleic acid can be complementary to an entire 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 coding strand, or to only a portion thereof. In one embodiment, an antisense nucleic acid molecule is antisense to a "coding region" of the coding strand of a nucleotide sequence
30 encoding a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351. The term "coding region" refers to the region of the nucleotide sequence comprising codons which are translated into amino acid residues. In another embodiment, the antisense nucleic acid molecule is antisense to a "noncoding region" of the coding strand of a nucleotide sequence

encoding 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351. The term "noncoding region" refers to 5' and 3' sequences which flank the coding region that are not translated into amino acids (also referred to as 5' and 3' untranslated regions).

- 5 [00232] Given the coding strand sequences encoding 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 disclosed herein, antisense nucleic acids of the invention can be designed according to the rules of Watson and Crick base pairing. The antisense nucleic acid molecule can be complementary to the entire coding region of 1435, 559, 10 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 mRNA, but more preferably is an oligonucleotide which is antisense to only a portion of the coding or noncoding region of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 mRNA. For example, the antisense 15 oligonucleotide can be complementary to the region surrounding the translation start site of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 mRNA. An antisense oligonucleotide can be, for example, about 5, 10, 15, 20, 25, 30, 35, 40, 45 or 50 nucleotides in length. An antisense nucleic acid of the invention can be constructed using 20 chemical synthesis and enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid (*e.g.*, an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, *e.g.*, 25 phosphorothioate derivatives and acridine substituted nucleotides can be used. Examples of modified nucleotides which can be used to generate the antisense nucleic acid include 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xantine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, 30 inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (*v*), wybutoxosine, pseudouracil, queosine, 2-

thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine. Alternatively, the antisense nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been subcloned in an antisense orientation (*i.e.*, RNA transcribed from the inserted

5 nucleic acid will be of an antisense orientation to a target nucleic acid of interest). Antisense nucleic acid molecules used in the methods of the invention are further described above, in section IV.

[00233] In yet another embodiment, the 1435, 559, 34021, 44099, 25278, 641, 260, 10 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 nucleic acid molecules used in the methods of the present invention can be modified at the base moiety, sugar moiety or phosphate backbone to improve, *e.g.*, the stability, hybridization, or solubility of the molecule. For example, the deoxyribose phosphate backbone of the nucleic acid molecules can be modified to generate peptide nucleic acids (see Hyrup B. *et al.* (1996) *Bioorganic & Medicinal Chemistry* 4 (1): 5-23). As used herein, the terms "peptide nucleic acids" or "PNAs" refer to nucleic acid mimics, *e.g.*, DNA mimics, in which the deoxyribose phosphate backbone is replaced by a pseudopeptide backbone and only the four natural nucleobases are retained. The neutral backbone of PNAs has been shown to allow for specific hybridization to DNA and RNA 15 under conditions of low ionic strength. The synthesis of PNA oligomers can be performed using standard solid phase peptide synthesis protocols as described in Hyrup B. *et al.* (1996) *supra*; Perry-O'Keefe *et al.* (1996) *Proc. Natl. Acad. Sci.* 93:14670-675.

[00234] PNAs of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 nucleic acid 25 molecules can be used in the therapeutic and diagnostic applications described herein. For example, PNAs can be used as antisense or antigene agents for sequence-specific modulation of gene expression by, for example, inducing transcription or translation arrest or inhibiting replication. PNAs of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 30 6351 nucleic acid molecules can also be used in the analysis of single base pair mutations in a gene, (*e.g.*, by PNA-directed PCR clamping); as 'artificial restriction enzymes' when used in combination with other enzymes, (*e.g.*, S1 nucleases (Hyrup B. *et al.* (1996) *supra*)); or as probes or primers for DNA sequencing or hybridization (Hyrup B. *et al.* (1996) *supra*; Perry-O'Keefe *et al.* (1996) *supra*).

[00235] In another embodiment, PNAs of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 can be modified, (e.g., to enhance their stability or cellular uptake), by attaching lipophilic or other helper groups to PNA, by the formation of PNA-DNA
5 chimeras, or by the use of liposomes or other techniques of drug delivery known in the art. For example, PNA-DNA chimeras of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 nucleic acid molecules can be generated which may combine the advantageous properties of PNA and DNA. Such chimeras allow DNA recognition enzymes, (e.g.,
10 RNase H and DNA polymerases), to interact with the DNA portion while the PNA portion would provide high binding affinity and specificity. PNA-DNA chimeras can be linked using linkers of appropriate lengths selected in terms of base stacking, number of bonds between the nucleobases, and orientation (Hyrup B. *et al.* (1996) *supra*). The synthesis of PNA-DNA chimeras can be performed as described in Hyrup B. *et al.* (1996) *supra* and
15 Finn P.J. *et al.* (1996) *Nucleic Acids Res.* 24 (17): 3357-63. For example, a DNA chain can be synthesized on a solid support using standard phosphoramidite coupling chemistry and modified nucleoside analogs, e.g., 5'-(4-methoxytrityl)amino-5'-deoxy-thymidine phosphoramidite, can be used as a between the PNA and the 5' end of DNA (Mag, M. *et al.* (1989) *Nucleic Acid Res.* 17: 5973-88). PNA monomers are then coupled in a stepwise
20 manner to produce a chimeric molecule with a 5' PNA segment and a 3' DNA segment (Finn P.J. *et al.* (1996) *supra*). Alternatively, chimeric molecules can be synthesized with a 5' DNA segment and a 3' PNA segment (Peterser, K.H. *et al.* (1975) *Bioorganic Med. Chem. Lett.* 5: 1119-11124).

[00236] In other embodiments, the oligonucleotide used in the methods of the
25 invention may include other appended groups such as peptides (e.g., for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (see, e.g., Letsinger *et al.* (1989) *Proc. Natl. Acad. Sci. USA* 86:6553-6556; Lemaitre *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:648-652; PCT Publication No. W088/09810) or the blood-brain barrier (see, e.g., PCT Publication No. W089/10134). In addition, oligonucleotides
30 can be modified with hybridization-triggered cleavage agents (See, e.g., Krol *et al.* (1988) *Bio-Techniques* 6:958-976) or intercalating agents. (See, e.g., Zon (1988) *Pharm. Res.* 5:539-549). To this end, the oligonucleotide may be conjugated to another molecule, (e.g., a peptide, hybridization triggered cross-linking agent, transport agent, or hybridization-triggered cleavage agent).

Isolated 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 Proteins and Anti-1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 Antibodies Used in the Methods of
the Invention

[00237] The methods of the invention include the use of isolated 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 proteins, and biologically active portions thereof, as well as polypeptide fragments suitable for use as immunogens to raise anti-1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 antibodies. In one embodiment, native 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 proteins can be isolated from cells or tissue sources by an appropriate purification scheme using standard protein purification techniques. In another embodiment, 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 proteins are produced by recombinant DNA techniques. Alternative to recombinant expression, a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein or polypeptide can be synthesized chemically using standard peptide synthesis techniques.

[00238] As used herein, a "biologically active portion" of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein includes a fragment of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein having a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 activity. Biologically active portions of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein include peptides comprising amino acid sequences sufficiently identical to or derived from the amino acid sequence of the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein, e.g., the amino acid sequences shown in SEQ ID NO:2, 5, 8, 11, 14, 17, 20, 23, 26, 29, 32, 35, 38, 41, 44, 47, 50, 53, 56, 59, 62 or 65 which include fewer amino acids than the full length 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303,

985, 13237, 13601, 18926, 318, 2058 or 6351 proteins, and exhibit at least one activity of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein. Typically, biologically active portions comprise a domain or motif with at least one activity of the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein (*e.g.*, the N-terminal region of the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein that is believed to be involved in the regulation of apoptotic activity). A biologically active portion of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein can be a polypeptide which is, for example, 25, 50, 75, 100, 125, 150, 175, 200, 250, 300 or more amino acids in length. Biologically active portions of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein can be used as targets for developing agents which modulate a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 activity.

[00239] In a preferred embodiment, the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein used in the methods of the invention has an amino acid sequence shown in SEQ ID NO:2, 5, 8, 11, 14, 17, 20, 23, 26, 29, 32, 35, 38, 41, 44, 47, 50, 53, 56, 59, 62 or 65, respectively. In other embodiments, the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein is substantially identical to SEQ ID NO:2, 5, 8, 11, 14, 17, 20, 23, 26, 29, 32, 35, 38, 41, 44, 47, 50, 53, 56, 59, 62 or 65, respectively, and retains the functional activity of the protein of SEQ ID NO:2, 5, 8, 11, 14, 17, 20, 23, 26, 29, 32, 35, 38, 41, 44, 47, 50, 53, 56, 59, 62 or 65, yet differs in amino acid sequence due to natural allelic variation or mutagenesis, as described in detail in subsection V above. Accordingly, in another embodiment, the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein used in the methods of the invention is a protein which comprises an amino acid sequence at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more identical to SEQ ID NO:2, 5, 8, 11, 14, 17, 20, 23, 26, 29, 32, 35, 38, 41, 44, 47, 50, 53, 56, 59, 62 or 65.

[00240] To determine the percent identity of two amino acid sequences or of two nucleic acid sequences, the sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in one or both of a first and a second amino acid or nucleic acid sequence for optimal alignment and non-identical sequences can be disregarded for comparison purposes). In a preferred embodiment, the length of a reference sequence aligned for comparison purposes is at least 30%, preferably at least 40%, more preferably at least 50%, even more preferably at least 60%, and even more preferably at least 70%, 80%, or 90% of the length of the reference sequence (*e.g.*, when aligning a second sequence to the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 amino acid sequence of SEQ ID NO:2, 5, 8, 11, 14, 17, 20, 23, 26, 29, 32, 35, 38, 41, 44, 47, 50, 53, 56, 59, 62 or 65, having 500 amino acid residues, at least 75, preferably at least 150, more preferably at least 225, even more preferably at least 300, and even more preferably at least 400 or more amino acid residues are aligned). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position (as used herein amino acid or nucleic acid "identity" is equivalent to amino acid or nucleic acid "homology"). The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences.

[00241] The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. In a preferred embodiment, the percent identity between two amino acid sequences is determined using the Needleman and Wunsch (*J. Mol. Biol.* 48:444-453 (1970)) algorithm which has been incorporated into the GAP program in the GCG software package, using either a Blosum 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6. In yet another preferred embodiment, the percent identity between two nucleotide sequences is determined using the GAP program in the GCG software package, using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. In another embodiment, the percent identity between two amino acid or nucleotide sequences is determined using the algorithm of E. Meyers and W. Miller (*Comput. Appl. Biosci.* 4:11-17 (1988)) which has been incorporated

into the ALIGN program (version 2.0 or 2.0U), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4.

[00242] The methods of the invention may also use 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 chimeric or fusion proteins. As used herein, a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 "chimeric protein" or "fusion protein" comprises a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 polypeptide operatively linked to a non-1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 polypeptide. An "1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 polypeptide" refers to a polypeptide having an amino acid sequence corresponding to a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 molecule, whereas a "non-1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 polypeptide" refers to a polypeptide having an amino acid sequence corresponding to a protein which is not substantially homologous to the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein, *e.g.*, a protein which is different from the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein and which is derived from the same or a different organism. Within a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 fusion protein the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 polypeptide can correspond to all or a portion of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein. In a preferred embodiment, a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 fusion protein comprises at least one biologically active portion of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein. In another preferred

embodiment, a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 fusion protein comprises at least two biologically active portions of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein. Within the fusion protein, the term "operatively linked" is intended to indicate that the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 polypeptide and the non-1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 polypeptide are fused in-frame to each other. The non-1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 polypeptide can be fused to the N-terminus or C-terminus of the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 polypeptide.

[00243] For example, in one embodiment, the fusion protein is a GST-1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 fusion protein in which the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 sequences are fused to the C-terminus of the GST sequences. Such fusion proteins can facilitate the purification of recombinant 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351.

[00244] In another embodiment, this fusion protein is a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein containing a heterologous signal sequence at its N-terminus. In certain host cells (*e.g.*, mammalian host cells), expression and/or secretion of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 can be increased through use of a heterologous signal sequence.

[00245] The 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 fusion proteins used in the methods of the invention can be incorporated into pharmaceutical compositions and administered to a subject *in vivo*. The 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601,

18926, 318, 2058 or 6351 fusion proteins can be used to affect the bioavailability of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 substrate. Use of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 fusion proteins may be useful therapeutically for the treatment of disorders caused by, for example, (i) aberrant modification or mutation of a gene encoding a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein; (ii) mis-regulation of the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 gene; and (iii) aberrant post-translational modification of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein.

[00246] Moreover, the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 - fusion proteins used in the methods of the invention can be used as immunogens to produce anti-1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 antibodies in a subject, to purify 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 ligands and in screening assays to identify molecules which inhibit the interaction of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 with a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 substrate.

[00247] Preferably, a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 chimeric or fusion protein used in the methods of the invention is produced by standard recombinant DNA techniques. For example, DNA fragments coding for the different polypeptide sequences are ligated together in-frame in accordance with conventional techniques, for example by employing blunt-ended or stagger-ended termini for ligation, restriction enzyme digestion to provide for appropriate termini, filling-in of cohesive ends as appropriate, alkaline phosphatase treatment to avoid undesirable joining, and enzymatic ligation. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of

gene fragments can be carried out using anchor primers which give rise to complementary overhangs between two consecutive gene fragments which can subsequently be annealed and reamplified to generate a chimeric gene sequence (see, for example, *Current Protocols in Molecular Biology*, eds. Ausubel *et al.* John Wiley & Sons: 1992). Moreover, many
5 expression vectors are commercially available that already encode a fusion moiety (*e.g.*, a GST polypeptide). A 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 -encoding nucleic acid can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032,
10 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein.

[00248] The present invention also pertains to the use of variants of the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 proteins which function as either 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303,
15 985, 13237, 13601, 18926, 318, 2058 or 6351 agonists (mimetics) or as 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 antagonists. Variants of the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 proteins can be generated by mutagenesis, *e.g.*,
20 discrete point mutation or truncation of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein. An agonist of the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 proteins can retain substantially the same, or a subset, of the biological activities of
25 the naturally occurring form of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein. An antagonist of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein can inhibit one or more of the activities of the naturally occurring form of the 1435,
30 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein by, for example, competitively modulating a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 -mediated activity of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032,

46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein.

Thus, specific biological effects can be elicited by treatment with a variant of limited function. In one embodiment, treatment of a subject with a variant having a subset of the biological activities of the naturally occurring form of the protein has fewer side effects in
5 a subject relative to treatment with the naturally occurring form of the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein.

[00249] In one embodiment, variants of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein which function as either 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 agonists (mimetics) or as 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 antagonists can be identified by screening combinatorial libraries of mutants, *e.g.*,
10 truncation mutants, of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein for 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein agonist or antagonist activity. In one embodiment, a variegated library of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 variants is generated by combinatorial mutagenesis at the nucleic acid level and is encoded by a variegated gene library. A variegated library of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 variants can be produced by, for example,
25 enzymatically ligating a mixture of synthetic oligonucleotides into gene sequences such that a degenerate set of potential 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 sequences is expressible as individual polypeptides, or alternatively, as a set of larger fusion proteins (*e.g.*, for phage display) containing the set of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 sequences therein. There are a variety of methods which can be used to produce libraries of potential 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 variants from a degenerate oligonucleotide sequence. Chemical synthesis of
30

a degenerate gene sequence can be performed in an automatic DNA synthesizer, and the synthetic gene then ligated into an appropriate expression vector. Use of a degenerate set of genes allows for the provision, in one mixture, of all of the sequences encoding the desired set of potential 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 sequences. Methods for synthesizing degenerate oligonucleotides are known in the art (see, *e.g.*, Narang, S.A. (1983) *Tetrahedron* 39:3; Itakura *et al.* (1984) *Annu. Rev. Biochem.* 53:323; Itakura *et al.* (1984) *Science* 198:1056; Ike *et al.* (1983) *Nucleic Acid Res.* 11:477).

[00250] In addition, libraries of fragments of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein coding sequence can be used to generate a variegated population of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 fragments for screening and subsequent selection of variants of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein. In one embodiment, a library of coding sequence fragments can be generated by treating a double stranded PCR fragment of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 coding sequence with a nuclease under conditions wherein nicking occurs only about once per molecule, denaturing the double stranded DNA, renaturing the DNA to form double stranded DNA which can include sense/antisense pairs from different nicked products, removing single stranded portions from reformed duplexes by treatment with S1 nuclease, and ligating the resulting fragment library into an expression vector. By this method, an expression library can be derived which encodes N-terminal, C-terminal and internal fragments of various sizes of the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein.

[00251] Several techniques are known in the art for screening gene products of combinatorial libraries made by point mutations or truncation, and for screening cDNA libraries for gene products having a selected property. Such techniques are adaptable for rapid screening of the gene libraries generated by the combinatorial mutagenesis of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 proteins. The most widely used techniques, which are amenable to high through-put analysis, for screening large gene

libraries typically include cloning the gene library into replicable expression vectors, transforming appropriate cells with the resulting library of vectors, and expressing the combinatorial genes under conditions in which detection of a desired activity facilitates isolation of the vector encoding the gene whose product was detected. Recursive ensemble
5 mutagenesis (REM), a new technique which enhances the frequency of functional mutants in the libraries, can be used in combination with the screening assays to identify 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 variants (Arkin and Yourvan (1992) *Proc. Natl. Acad. Sci. USA* 89:7811-7815; Delgrave *et al.* (1993) *Protein Engineering* 6(3):327-
10 331).

[00252] The methods of the present invention further include the use of anti-1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 antibodies. An isolated 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein, or a portion or fragment thereof, can
15 be used as an immunogen to generate antibodies that bind 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 using standard techniques for polyclonal and monoclonal antibody preparation. A full-length 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or
20 6351 protein can be used or, alternatively, antigenic peptide fragments of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 can be used as immunogens. The antigenic peptide of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 comprises at least 8 amino
25 acid residues of the amino acid sequence shown in SEQ ID NO:2, 5, 8, 11, 14, 17, 20, 23, 26, 29, 32, 35, 38, 41, 44, 47, 50, 53, 56, 59, 62 or 65, and encompasses an epitope of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 such that an antibody raised against
30 the peptide forms a specific immune complex with the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein. Preferably, the antigenic peptide comprises at least 10 amino acid residues, more preferably at least 15 amino acid residues, even more preferably at least 20 amino acid residues, and most preferably at least 30 amino acid residues.

[00253] Preferred epitopes encompassed by the antigenic peptide are regions of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 that are located on the surface of the protein, *e.g.*, hydrophilic regions, as well as regions with high antigenicity.

5 [00254] A 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 immunogen is typically used to prepare antibodies by immunizing a suitable subject, (*e.g.*, rabbit, goat, mouse, or other mammal) with the immunogen. An appropriate immunogenic preparation can contain, for example, recombinantly expressed 1435, 559, 34021, 44099, 25278, 641,
10 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein or a chemically synthesized 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 polypeptide. The preparation can further include an adjuvant, such as Freund's complete or incomplete adjuvant, or similar immunostimulatory agent.
15 Immunization of a suitable subject with an immunogenic 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 preparation induces a polyclonal anti-1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 antibody response.

20 [00255] The term "antibody" as used herein refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, *i.e.*, molecules that contain an antigen binding site which specifically binds (immunoreacts with) an antigen, such as a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351. Examples of immunologically
25 active portions of immunoglobulin molecules include F(ab) and F(ab)₂ fragments which can be generated by treating the antibody with an enzyme such as pepsin. The invention provides polyclonal and monoclonal antibodies that bind 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 molecules. The term "monoclonal antibody" or "monoclonal
30 antibody composition", as used herein, refers to a population of antibody molecules that contain only one species of an antigen binding site capable of immunoreacting with a particular epitope of 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351. A monoclonal antibody composition thus typically displays a single binding affinity for a

particular 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein with which it immunoreacts.

[00256] Polyclonal anti-1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 antibodies can be prepared as described above by immunizing a suitable subject with a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 immunogen. The anti-1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 antibody titer in the immunized subject can be monitored over time by standard techniques, such as with an enzyme linked immunosorbent assay (ELISA) using immobilized 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351. If desired, the antibody molecules directed against 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 can be isolated from the mammal (*e.g.*, from the blood) and further purified by well known techniques, such as protein A chromatography to obtain the IgG fraction. At an appropriate time after immunization, *e.g.*, when the anti-1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 antibody titers are highest, antibody-producing cells can be obtained from the subject and used to prepare monoclonal antibodies by standard techniques, such as the hybridoma technique originally described by Kohler and Milstein (1975) *Nature* 256:495-497) (see also, Brown *et al.* (1981) *J. Immunol.* 127:539-46; Brown *et al.* (1980) *J. Biol. Chem.* 255:4980-83; Yeh *et al.* (1976) *Proc. Natl. Acad. Sci. USA* 76:2927-31; and Yeh *et al.* (1982) *Int. J. Cancer* 29:269-75), the more recent human B cell hybridoma technique (Kozbor *et al.* (1983) *Immunol Today* 4:72), the EBV-hybridoma technique (Cole *et al.* (1985) *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc., pp. 77-96) or trioma techniques. The technology for producing monoclonal antibody hybridomas is well known (see generally Kenneth, R. H. in *Monoclonal Antibodies: A New Dimension In Biological Analyses*, Plenum Publishing Corp., New York, New York (1980); Lerner, E. A. (1981) *Yale J. Biol. Med.* 54:387-402; Gefter, M. L. *et al.* (1977) *Somatic Cell Genet.* 3:231-36). Briefly, an immortal cell line (typically a myeloma) is fused to lymphocytes (typically splenocytes) from a mammal immunized with a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656,

62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 immunogen as described above, and the culture supernatants of the resulting hybridoma cells are screened to identify a hybridoma producing a monoclonal antibody that binds 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 .

[00257] Any of the many well known protocols used for fusing lymphocytes and immortalized cell lines can be applied for the purpose of generating an anti-1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 monoclonal antibody (see, *e.g.*, G. Galfre *et al.* (1977) *Nature* 266:55052; Gefter *et al.* (1977) *supra*; Lerner (1981) *supra*; and Kenneth (1980) *supra*). Moreover, the ordinarily skilled worker will appreciate that there are many variations of such methods which also would be useful. Typically, the immortal cell line (*e.g.*, a myeloma cell line) is derived from the same mammalian species as the lymphocytes. For example, murine hybridomas can be made by fusing lymphocytes from a mouse immunized with an immunogenic preparation of the present invention with an immortalized mouse cell line. Preferred immortal cell lines are mouse myeloma cell lines that are sensitive to culture medium containing hypoxanthine, aminopterin and thymidine ("HAT medium"). Any of a number of myeloma cell lines can be used as a fusion partner according to standard techniques, *e.g.*, the P3-NS1/1-Ag4-1, P3-x63-Ag8.653 or Sp2/O-Ag14 myeloma lines. These myeloma lines are available from ATCC. Typically, HAT-sensitive mouse myeloma cells are fused to mouse splenocytes using polyethylene glycol ("PEG"). Hybridoma cells resulting from the fusion are then selected using HAT medium, which kills unfused and unproductively fused myeloma cells (unfused splenocytes die after several days because they are not transformed). Hybridoma cells producing a monoclonal antibody of the invention are detected by screening the hybridoma culture supernatants for antibodies that bind 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 , *e.g.*, using a standard ELISA assay.

[00258] Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal anti-1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 antibody can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (*e.g.*, an antibody phage display library) with 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318,

2058 or 6351 to thereby isolate immunoglobulin library members that bind 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351. Kits for generating and screening phage display libraries are commercially available (e.g., the Pharmacia *Recombinant Phage Antibody System*, Catalog No. 27-9400-01; and the Stratagene *SurfZAP™ Phage Display Kit*, Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody display library can be found in, for example, Ladner *et al.* U.S. Patent No. 5,223,409; Kang *et al.* PCT International Publication No. WO 92/18619; Dower *et al.* PCT International Publication No. WO 91/17271; Winter *et al.* PCT International Publication WO 92/20791; Markland *et al.* PCT International Publication No. WO 92/15679; Breitling *et al.* PCT International Publication WO 93/01288; McCafferty *et al.* PCT International Publication No. WO 92/01047; Garrard *et al.* PCT International Publication No. WO 92/09690; Ladner *et al.* PCT International Publication No. WO 90/02809; Fuchs *et al.* (1991) *Bio/Technology* 9:1370-1372; Hay *et al.* (1992) *Hum. Antibod. Hybridomas* 3:81-85; Huse *et al.* (1989) *Science* 246:1275-1281; Griffiths *et al.* (1993) *EMBO J* 12:725-734; Hawkins *et al.* (1992) *J. Mol. Biol.* 226:889-896; Clarkson *et al.* (1991) *Nature* 352:624-628; Gram *et al.* (1992) *Proc. Natl. Acad. Sci. USA* 89:3576-3580; Garrad *et al.* (1991) *Bio/Technology* 9:1373-1377; Hoogenboom *et al.* (1991) *Nuc. Acid Res.* 19:4133-4137; Barbas *et al.* (1991) *Proc. Natl. Acad. Sci. USA* 88:7978-7982; and McCafferty *et al.* (1990) *Nature* 348:552-554.

[00259] Additionally, recombinant anti-1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 antibodies, such as chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, which can be made using standard recombinant DNA techniques, are within the scope of the methods of the invention. Such chimeric and humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art, for example using methods described in Robinson *et al.* International Application No. PCT/US86/02269; Akira, *et al.* European Patent Application 184,187; Taniguchi, M., European Patent Application 171,496; Morrison *et al.* European Patent Application 173,494; Neuberger *et al.* PCT International Publication No. WO 86/01533; Cabilly *et al.* U.S. Patent No. 4,816,567; Cabilly *et al.* European Patent Application 125,023; Better *et al.* (1988) *Science* 240:1041-1043; Liu *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:3439-3443; Liu *et al.* (1987) *J. Immunol.* 139:3521-3526; Sun *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:214-218; Nishimura *et al.* (1987) *Canc. Res.*

47:999-1005; Wood *et al.* (1985) *Nature* 314:446-449; Shaw *et al.* (1988) *J. Natl. Cancer Inst.* 80:1553-11435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351; Morrison, S. L. (1985) *Science* 229:1202-1207; Oi *et al.* (1986) *BioTechniques* 4:214; Winter U.S. Patent 5,225,539; Jones *et al.* (1986) *Nature* 321:552-525; Verhoeyan *et al.* (1988) *Science* 239:1534; and Beidler *et al.* (1988) *J. Immunol.* 141:4053-4060.

[00260] An anti-1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 antibody can be used to detect 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein (*e.g.*, in a cellular lysate or cell supernatant) in order to evaluate the abundance and pattern of expression of the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 protein. Anti-1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 antibodies can be used diagnostically to monitor protein levels in tissue as part of a clinical testing procedure, *e.g.*, to, for example, determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling (*i.e.*, physically linking) the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β -galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ^{125}I , ^{131}I , ^{35}S or ^3H .

[00261] This invention is further illustrated by the following examples which should not be construed as limiting. The contents of all references, patents and published patent applications cited throughout this application, as well as the Figure and the Sequence Listing is incorporated herein by reference.

EXAMPLES**EXAMPLE 1: TISSUE DISTRIBUTION OF USING TAQMAN™ ANALYSIS**

5 **[00262]** This example describes the TaqMan™ procedure. The Taqman™ procedure is a quantitative, reverse transcription PCR-based approach for detecting mRNA. The RT-PCR reaction exploits the 5' nuclease activity of AmpliTaq Gold™ DNA Polymerase to cleave a TaqMan™ probe during PCR. Briefly, cDNA was generated from the samples of interest, *e.g.*, heart, kidney, liver, skeletal muscle, and various vessels, and
10 used as the starting material for PCR amplification. In addition to the 5' and 3' gene-specific primers, a gene-specific oligonucleotide probe (complementary to the region being amplified) was included in the reaction (*i.e.*, the Taqman™ probe). The TaqMan™ probe includes the oligonucleotide with a fluorescent reporter dye covalently linked to the 5' end of the probe (such as FAM (6-carboxyfluorescein), TET (6-carboxy-4,7,2',7'-
15 tetrachlorofluorescein), JOE (6-carboxy-4,5-dichloro-2,7-dimethoxyfluorescein), or VIC) and a quencher dye (TAMRA (6-carboxy-N,N,N',N'-tetramethylrhodamine) at the 3' end of the probe.

[00263] During the PCR reaction, cleavage of the probe separates the reporter dye and the quencher dye, resulting in increased fluorescence of the reporter. Accumulation of
20 PCR products is detected directly by monitoring the increase in fluorescence of the reporter dye. When the probe is intact, the proximity of the reporter dye to the quencher dye results in suppression of the reporter fluorescence. During PCR, if the target of interest is present, the probe specifically anneals between the forward and reverse primer sites. The 5'-3' nucleolytic activity of the AmpliTaq™ Gold DNA Polymerase cleaves the probe between
25 the reporter and the quencher only if the probe hybridizes to the target. The probe fragments are then displaced from the target, and polymerization of the strand continues. The 3' end of the probe is blocked to prevent extension of the probe during PCR. This process occurs in every cycle and does not interfere with the exponential accumulation of product. RNA was prepared using the trizol method and treated with DNase to remove
30 contaminating genomic DNA. cDNA was synthesized using standard techniques. Mock cDNA synthesis in the absence of reverse transcriptase resulted in samples with no detectable PCR amplification of the control gene confirms efficient removal of genomic DNA contamination.

[00264] Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following

5 claims.

What is claimed:

1. A method for identifying a compound capable of treating a urological disorder, comprising assaying the ability of the compound to modulate 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 nucleic acid expression or 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 polypeptide activity, thereby identifying a compound capable of treating a urological disorder.
10
2. A method for identifying a compound capable of modulating a hyperplasia comprising:
 - a) contacting a cell which expresses 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 with a test compound; and
15
 - b) assaying the ability of the test compound to modulate the expression of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 nucleic acid or the activity of a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 polypeptide, thereby identifying a compound capable of modulating hyperplasia.
20
3. A method for modulating hyperplasia in a cell comprising contacting a cell with a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 modulator, thereby modulating hyperplasia in the cell.
25
4. The method of claim 2, wherein the cell is a bladder cell or a prostate cell.
30
5. The method of claim 3, wherein the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 modulator is a small organic molecule, peptide, antibody or antisense nucleic acid molecule.

6. The method of claim 3, wherein the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 modulator is capable of modulating 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 polypeptide activity.

7. The method of claim 6, wherein the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 modulator is a small organic molecule, peptide, antibody or antisense nucleic acid molecule.

8. The method of claim 6, wherein the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 modulator is capable of modulating 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 nucleic acid expression.

9. A method for treating a subject having a urological disorder characterized by aberrant 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 polypeptide activity or aberrant 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 nucleic acid expression comprising administering to the subject a 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 modulator, thereby treating said subject having a urological disorder.

10. The method of claim 9, wherein said urological disorder includes urinary incontinence including overactive/oversensitive bladder, overflow urinary incontinence, stress urinary incontinence caused by dysfunction of the bladder, urethra or central/peripheral nervous system, prostatitis, benign prostatic hyperplasia, cancer of the prostate, and kidney disorders.

11. The method of claim 9, wherein said 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 modulator is administered in a pharmaceutically acceptable formulation.

5

12. The method of claim 9, wherein the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 modulator is a small organic molecule, peptide, antibody or antisense nucleic acid molecule.

10

13. The method of claim 9, wherein the 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 modulator is capable of modulating 1435, 559, 34021, 44099, 25278, 641, 260, 55089, 21407, 42032, 46656, 62553, 302, 323, 12303, 985, 13237, 13601, 18926, 318, 2058 or 6351 polypeptide activity.

15

SEQUENCE LISTING

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 Silos-Santiago, Inmaculada
 Venkateswarlu, Karicheti

<120> METHODS AND COMPOSITIONS FOR TREATING
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tac gag gtc aaa tac tat gaa aag cag gaa caa gaa aca agt tat acc	1555
Tyr Glu Val Lys Tyr Tyr Glu Lys Gln Glu Gln Glu Thr Ser Tyr Thr	
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Ile Leu Arg Ala Arg Gly Thr Asn Val Thr Ile Ser Ser Leu Lys Pro	
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gac act ata tac gta ttc caa atc cga gcc cga aca gcc gct gga tat	1651
Asp Thr Ile Tyr Val Phe Gln Ile Arg Ala Arg Thr Ala Ala Gly Tyr	
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Gly Thr Asn Ser Arg Lys Phe Glu Phe Glu Thr Ser Pro Asp Ser Phe	
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Ser Ile Ser Gly Glu Ser Ser Gln Val Val Met Ile Ala Ile Ser Ala	
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Ala Val Ala Ile Ile Leu Leu Thr Val Val Ile Tyr Val Leu Ile Gly	
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Arg Phe Cys Gly Tyr Lys Ser Lys His Gly Ala Asp Glu Lys Arg Leu	
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Asp	Pro	His	Thr	Tyr	Glu	Asp	Pro	Thr	Gln	Ala	Val	His	Glu	Phe	Ala	
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aag	gaa	ttg	gat	gcc	acc	aac	ata	tcc	att	gat	aaa	gtt	gtt	gga	gca	1987
Lys	Glu	Leu	Asp	Ala	Thr	Asn	Ile	Ser	Ile	Asp	Lys	Val	Val	Gly	Ala	
			615				620					625				
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Gly	Glu	Phe	Gly	Glu	Val	Cys	Ser	Gly	Arg	Leu	Lys	Leu	Pro	Ser	Lys	
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Lys	Glu	Ile	Ser	Val	Ala	Ile	Lys	Thr	Leu	Lys	Val	Gly	Tyr	Thr	Glu	
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Lys	Gln	Arg	Arg	Asp	Phe	Leu	Gly	Glu	Ala	Ser	Ile	Met	Gly	Gln	Phe	
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Asp	His	Pro	Asn	Ile	Ile	Arg	Leu	Glu	Gly	Val	Val	Thr	Lys	Ser	Lys	
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Pro	Val	Met	Ile	Val	Thr	Glu	Tyr	Met	Glu	Asn	Gly	Ser	Leu	Asp	Ser	
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Phe	Leu	Arg	Lys	His	Asp	Ala	Gln	Phe	Thr	Val	Ile	Gln	Leu	Val	Gly	
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Met	Leu	Arg	Gly	Ile	Ala	Ser	Gly	Met	Lys	Tyr	Leu	Ser	Asp	Met	Gly	
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Tyr	Val	His	Arg	Asp	Leu	Ala	Ala	Arg	Asn	Ile	Leu	Ile	Asn	Ser	Asn	
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Leu	Val	Cys	Lys	Val	Ser	Asp	Phe	Gly	Leu	Ser	Arg	Val	Leu	Glu	Asp	
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Asp	Pro	Glu	Ala	Ala	Tyr	Thr	Thr	Arg	Gly	Gly	Lys	Ile	Pro	Ile	Arg	
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Trp	Thr	Ser	Pro	Glu	Ala	Ile	Ala	Tyr	Arg	Lys	Phe	Thr	Ser	Ala	Ser	
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Asp	Val	Trp	Ser	Tyr	Gly	Ile	Val	Leu	Trp	Glu	Val	Met	Ser	Tyr	Gly	
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Glu	Arg	Pro	Tyr	Trp	Glu	Met	Ser	Asn	Gln	Asp	Val	Ile	Lys	Ala	Val	
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Leu Leu Asp Gln Ser Asn Val Asp Ile Ser Thr Phe Arg Thr Thr Gly			
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gac tgg ctt aat ggt gtc cgg aca gca cac tgc aag gaa atc ttc acg			2899
Asp Trp Leu Asn Gly Val Arg Thr Ala His Cys Lys Glu Ile Phe Thr			
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Gly Val Glu Tyr Ser Ser Cys Asp Thr Ile Ala Lys Ile Ser Thr Asp			
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Asp Met Lys Lys Val Gly Val Thr Val Val Gly Pro Gln Lys Lys Ile			
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Ile Ser Ser Ile Lys Ala Leu Glu Thr Gln Ser Lys Asn Gly Pro Val			
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Ser His Gly Trp Glu Glu Ile Ser Gly Val Asp Glu His Tyr Thr Pro			
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Val Ser Val Arg Val Tyr Phe Lys Lys Cys Pro Phe Thr Val Lys Asn			
195 200 205			
Leu Ala Met Phe Pro Asp Thr Val Pro Met Asp Ser Gln Ser Leu Val			

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Arg Met Tyr Cys Ser Thr	Glu Gly Glu Trp Leu	Val Pro Ile Gly Lys
245	250	255
Cys Ser Cys Asn Ala Gly	Tyr Glu Glu Arg Gly	Phe Met Cys Gln Ala
260	265	270
Cys Arg Pro Gly Phe Tyr	Lys Ala Leu Asp Gly	Asn Met Lys Cys Ala
275	280	285
Lys Cys Pro Pro His Ser	Ser Thr Gln Glu Asp	Gly Ser Met Asn Cys
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Arg Cys Glu Asn Asn Tyr	Phe Arg Ala Asp Lys	Asp Pro Pro Ser Met
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Ala Cys Thr Arg Pro Pro	Ser Ser Pro Arg Asn	Val Ile Ser Asn Ile
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Asn Glu Thr Ser Val Ile	Leu Asp Trp Ser Trp	Pro Leu Asp Thr Gly
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Gly Arg Lys Asp Val Thr	Phe Asn Ile Ile Cys	Lys Lys Cys Gly Trp
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Ala His Thr Asn Tyr Thr	Phe Glu Ile Asp Ala	Val Asn Gly Val Ser
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Glu Leu Ser Ser Pro Pro	Arg Gln Phe Ala Ala	Val Ser Ile Thr Thr
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Ser Arg Asn Ser Ile Ser	Leu Ser Trp Gln Glu	Pro Glu His Pro Asn
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Tyr Val Leu Ile Gly Arg	Phe Cys Gly Tyr Lys	Ser Lys His Gly Ala
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Asp Glu Lys Arg Leu His	Phe Gly Asn Gly His	Leu Lys Leu Pro Gly
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Leu Arg Thr Tyr Val Asp	Pro His Thr Tyr Glu	Asp Pro Thr Gln Ala
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Val His Glu Phe Ala Lys	Glu Leu Asp Ala Thr	Asn Ile Ser Ile Asp
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Lys Val Val Gly Ala Gly	Glu Phe Gly Glu Val	Cys Ser Gly Arg Leu
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Lys Leu Pro Ser Lys Lys	Glu Ile Ser Val Ala	Ile Lys Thr Leu Lys
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Val Gly Tyr Thr Glu Lys	Gln Arg Arg Asp Phe	Leu Gly Glu Ala Ser
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Ile Met Gly Gln Phe Asp	His Pro Asn Ile Ile	Arg Leu Glu Gly Val
675	680	685
Val Thr Lys Ser Lys Pro	Val Met Ile Val Thr	Glu Tyr Met Glu Asn
690	695	700
Gly Ser Leu Asp Ser Phe	Leu Arg Lys His Asp	Ala Gln Phe Thr Val
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Ile Gln Leu Val Gly Met	Leu Arg Gly Ile Ala	Ser Gly Met Lys Tyr
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Leu Ser Asp Met Gly Tyr	Val His Arg Asp Leu	Ala Ala Arg Asn Ile
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755	760	765

Arg Val Leu Glu Asp Asp Pro Glu Ala Ala Tyr Thr Thr Arg Gly Gly
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 Lys Ile Pro Ile Arg Trp Thr Ser Pro Glu Ala Ile Ala Tyr Arg Lys
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 Val Met Ser Tyr Gly Glu Arg Pro Tyr Trp Glu Met Ser Asn Gln Asp
 820 825 830
 Val Ile Lys Ala Val Asp Glu Gly Tyr Arg Leu Pro Pro Pro Met Asp
 835 840 845
 Cys Pro Ala Ala Leu Tyr Gln Leu Met Leu Asp Cys Trp Gln Lys Asp
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 Leu Ile Arg Asn Pro Gly Ser Leu Lys Ile Ile Thr Ser Ala Ala Ala
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 Arg Pro Ser Asn Leu Leu Leu Asp Gln Ser Asn Val Asp Ile Ser Thr
 900 905 910
 Phe Arg Thr Thr Gly Asp Trp Leu Asn Gly Val Arg Thr Ala His Cys
 915 920 925
 Lys Glu Ile Phe Thr Gly Val Glu Tyr Ser Ser Cys Asp Thr Ile Ala
 930 935 940
 Lys Ile Ser Thr Asp Asp Met Lys Lys Val Gly Val Thr Val Val Gly
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 Asp Ser Phe Gly Glu Leu Ile Pro Gln Pro Ser Asn Glu Val Asn Leu 30
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 ctg gat tca aaa aca att caa ggg gag ctg ggc tgg atc tct tat cca 144
 Leu Asp Ser Lys Thr Ile Gln Gly Glu Leu Gly Trp Ile Ser Tyr Pro 45
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 Ser His Gly Trp Glu Glu Ile Ser Gly Val Asp Glu His Tyr Thr Pro 60
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 Ile Arg Thr Tyr Gln Val Cys Asn Val Met Asp His Ser Gln Asn Asn 80
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 Trp Leu Arg Thr Asn Trp Val Pro Arg Asn Ser Ala Gln Lys Ile Tyr 95
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 gtg gag ctc aag ttc act cta cga gac tgc aat agc att cca ttg gtt 336
 Val Glu Leu Lys Phe Thr Leu Arg Asp Cys Asn Ser Ile Pro Leu Val 110
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Leu	Gly	Thr	Cys	Lys	Glu	Thr	Phe	Asn	Leu	Tyr	Tyr	Met	Glu	Ser	Asp		
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Asp	Asp	His	Gly	Val	Lys	Phe	Arg	Glu	His	Gln	Phe	Thr	Lys	Ile	Asp		
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Thr	Ile	Ala	Ala	Asp	Glu	Ser	Phe	Thr	Gln	Met	Asp	Leu	Gly	Asp	Arg		
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Ile	Leu	Lys	Leu	Asn	Thr	Glu	Ile	Arg	Glu	Val	Gly	Pro	Val	Asn	Lys		
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aag	gga	ttt	tat	ttg	gca	ttt	caa	gat	ggt	ggg	gct	tgt	gtt	gcc	ttg	576	
Lys	Gly	Phe	Tyr	Leu	Ala	Phe	Gln	Asp	Val	Gly	Ala	Cys	Val	Ala	Leu		
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Val	Ser	Val	Arg	Val	Tyr	Phe	Lys	Lys	Cys	Pro	Phe	Thr	Val	Lys	Asn		
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gtt acc aaa agt aag cca gtt atg att gtc aca gaa tac atg gag aat Val Thr Lys Ser Lys Pro Val Met Ile Val Thr Glu Tyr Met Glu Asn 690 695 700	2112
ggt tcc ttg gat agt ttc cta cgt aaa cac gat gcc cag ttt act gtc Gly Ser Leu Asp Ser Phe Leu Arg Lys His Asp Ala Gln Phe Thr Val 705 710 715 720	2160
att cag cta gtg ggg atg ctt cga ggg ata gca tct ggc atg aag tac Ile Gln Leu Val Gly Met Leu Arg Gly Ile Ala Ser Gly Met Lys Tyr 725 730 735	2208
ctg tca gac atg ggc tat gtt cac cga gac ctc gct gct cgg aac atc Leu Ser Asp Met Gly Tyr Val His Arg Asp Leu Ala Ala Arg Asn Ile 740 745 750	2256
ttg atc aac agt aac ttg gtg tgt aag gtt tct gat ttc gga ctt tcg Leu Ile Asn Ser Asn Leu Val Cys Lys Val Ser Asp Phe Gly Leu Ser 755 760 765	2304
cgt gtc ctg gag gat gac cca gaa gct gct tat aca aca aga gga ggg Arg Val Leu Glu Asp Asp Pro Glu Ala Ala Tyr Thr Thr Arg Gly Gly 770 775 780	2352
aag atc cca atc agg tgg aca tca cca gaa gct ata gcc tac cgc aag Lys Ile Pro Ile Arg Trp Thr Ser Pro Glu Ala Ile Ala Tyr Arg Lys 785 790 795 800	2400
ttc acg tca gcc agc gat gta tgg agt tat ggg att gtt ctc tgg gag Phe Thr Ser Ala Ser Asp Val Trp Ser Tyr Gly Ile Val Leu Trp Glu 805 810 815	2448
gtg atg tct tat gga gag aga cca tac tgg gag atg tcc aat cag gat Val Met Ser Tyr Gly Glu Arg Pro Tyr Trp Glu Met Ser Asn Gln Asp 820 825 830	2496
gta att aaa gct gta gat gag ggc tat cga ctg cca ccc ccc atg gac Val Ile Lys Ala Val Asp Glu Gly Tyr Arg Leu Pro Pro Pro Met Asp 835 840 845	2544
tgc cca gct gcc ttg tat cag ctg atg ctg gac tgc tgg cag aaa gac Cys Pro Ala Ala Leu Tyr Gln Leu Met Leu Asp Cys Trp Gln Lys Asp 850 855 860	2592
agg aac aac aga ccc aag ttt gag cag att gtt agt att ctg gac aag Arg Asn Asn Arg Pro Lys Phe Glu Gln Ile Val Ser Ile Leu Asp Lys 865 870 875 880	2640
ctt atc cgg aat ccc ggc agc ctg aag atc atc acc agt gca gcc gca Leu Ile Arg Asn Pro Gly Ser Leu Lys Ile Ile Thr Ser Ala Ala Ala 885 890 895	2688
agg cca tca aac ctt ctt ctg gac caa agc aat gtg gat atc tct acc Arg Pro Ser Asn Leu Leu Leu Asp Gln Ser Asn Val Asp Ile Ser Thr 900 905 910	2736
ttc cgc aca aca ggt gac tgg ctt aat ggt gtc cgg aca gca cac tgc Phe Arg Thr Thr Gly Asp Trp Leu Asn Gly Val Arg Thr Ala His Cys 915 920 925	2784
aag gaa atc ttc acg ggc gtg gag tac agt tct tgt gac aca ata gcc Lys Glu Ile Phe Thr Gly Val Glu Tyr Ser Ser Cys Asp Thr Ile Ala 930 935 940	2832

aag att tcc aca gat gac atg aaa aag gtt ggt gtc acc gtg gtt ggg 2880
 Lys Ile Ser Thr Asp Asp Met Lys Lys Val Gly Val Thr Val Val Gly
 945 950 955 960

cca cag aag aag atc atc agt agc att aaa gct cta gaa acg caa tca 2928
 Pro Gln Lys Lys Ile Ile Ser Ser Ile Lys Ala Leu Glu Thr Gln Ser
 965 970 975

aag aat ggc cca gtt ccc gtg taa 2952
 Lys Asn Gly Pro Val Pro Val *
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 gttaccacc ccgtcctcct aggggtgccct tgagccgcaa aactgctgtc cacgtggacc 180
 gggggtgaca tcgcacgtcc atctgccagg acccctgcgt ccaaattccg agac atg 237
 Met
 1

gcg acc aac ggc agc aag gtg gcc gac ggg cag atc tcc acc gag gtc 285
 Ala Thr Asn Gly Ser Lys Val Ala Asp Gly Gln Ile Ser Thr Glu Val
 5 10 15

agc gag gcc cct gtg gcc aat gac aag ccc aaa acc ttg gtg gtc aag 333
 Ser Glu Ala Pro Val Ala Asn Asp Lys Pro Lys Thr Leu Val Val Lys
 20 25 30

gtg cag aag aag gcg gca gac ctc ccc gac cgg gac acg tgg aag ggc 381
 Val Gln Lys Lys Ala Ala Asp Leu Pro Asp Arg Asp Thr Trp Lys Gly
 35 40 45

cgc ttc gac ttc ctc atg tcc tgt gtg ggc tat gcc atc ggc ctg ggc 429
 Arg Phe Asp Phe Leu Met Ser Cys Val Gly Tyr Ala Ile Gly Leu Gly
 50 55 60 65

aac gtc tgg agg ttc ccc tat ctc tgc ggg aaa aat ggt ggg gga gcc 477
 Asn Val Trp Arg Phe Pro Tyr Leu Cys Gly Lys Asn Gly Gly Gly Ala
 70 75 80

ttc ctg atc ccc tat ttc ctg aca ctc atc ttt gcg ggg gtc cca ctc 525
 Phe Leu Ile Pro Tyr Phe Leu Thr Leu Ile Phe Ala Gly Val Pro Leu
 85 90 95

ttc ctg ctg gag tgc tcc ctg ggc cag tac acc tcc atc ggg ggg cta 573
 Phe Leu Leu Glu Cys Ser Leu Gly Gln Tyr Thr Ser Ile Gly Gly Leu
 100 105 110

ggg gta tgg aag ctg gct cct atg ttc aag ggc gtg ggc ctt gcg gct 621
 Gly Val Trp Lys Leu Ala Pro Met Phe Lys Gly Val Gly Leu Ala Ala
 115 120 125

gct gtg cta tca ttc tgg ctg aac atc tac tac atc gtc atc atc tcc 669
 Ala Val Leu Ser Phe Trp Leu Asn Ile Tyr Tyr Ile Val Ile Ile Ser
 130 135 140 145

tgg gcc att tac tac ctg tac aac tcc ttc acc acg aca ctg ccg tgg 717
 Trp Ala Ile Tyr Tyr Leu Tyr Asn Ser Phe Thr Thr Thr Leu Pro Trp
 150 155 160

aaa cag tgc gac aac ccc tgg aac aca gac cgc tgc ttc tcc aac tac	765
Lys Gln Cys Asp Asn Pro Trp Asn Thr Asp Arg Cys Phe Ser Asn Tyr	
165 170 175	
agc atg gtc aac act acc aac atg acc agc gct gtg gtg gag ttc tgg	813
Ser Met Val Asn Thr Thr Asn Met Thr Ser Ala Val Val Glu Phe Trp	
180 185 190	
gag cgc aac atg cat cag atg acg gac ggg ctg gat aag cca ggt cag	861
Glu Arg Asn Met His Gln Met Thr Asp Gly Leu Asp Lys Pro Gly Gln	
195 200 205	
atc cgc tgg cca ctg gcc atc acg ctg gcc atc gcc tgg atc ctt gtg	909
Ile Arg Trp Pro Leu Ala Ile Thr Leu Ala Ile Ala Trp Ile Leu Val	
210 215 220 225	
tat ttc tgt atc tgg aag ggt gtt ggc tgg act gga aag gtg gtc tac	957
Tyr Phe Cys Ile Trp Lys Gly Val Gly Trp Thr Gly Lys Val Val Tyr	
230 235 240	
ttt tca gcc aca tac ccc tac atc atg ctg atc atc ctg ttc ttc cgt	1005
Phe Ser Ala Thr Tyr Pro Tyr Ile Met Leu Ile Ile Leu Phe Phe Arg	
245 250 255	
gga gtg acg ctg ccc ggg gcc aag gag ggc atc ctc ttc tac atc aca	1053
Gly Val Thr Leu Pro Gly Ala Lys Glu Gly Ile Leu Phe Tyr Ile Thr	
260 265 270	
ccc aac ttc cgc aag ctg tct gac tcc gag gtg tgg ctg gat gcg gca	1101
Pro Asn Phe Arg Lys Leu Ser Asp Ser Glu Val Trp Leu Asp Ala Ala	
275 280 285	
acc cag atc ttc ttc tca tac ggg ctg ggc ctg ggg tcc ctg atc gct	1149
Thr Gln Ile Phe Phe Ser Tyr Gly Leu Gly Leu Gly Ser Leu Ile Ala	
290 295 300 305	
ctc ggg agc tac aac tct ttc cac aac aat gtc tac agg gac tcc atc	1197
Leu Gly Ser Tyr Asn Ser Phe His Asn Asn Val Tyr Arg Asp Ser Ile	
310 315 320	
atc gtc tgc tgc atc aat tcg tgc acc agc atg ttc gca gga ttc gtc	1245
Ile Val Cys Cys Ile Asn Ser Cys Thr Ser Met Phe Ala Gly Phe Val	
325 330 335	
atc ttc tcc atc gtg ggc ttc atg gcc cat gtc acc aag agg tcc att	1293
Ile Phe Ser Ile Val Gly Phe Met Ala His Val Thr Lys Arg Ser Ile	
340 345 350	
gct gat gtg gcc gcc tca ggc ccc ggg ctg gcg ttc ctg gca tac cca	1341
Ala Asp Val Ala Ala Ser Gly Pro Gly Leu Ala Phe Leu Ala Tyr Pro	
355 360 365	
gag gcg gtg acc cag ctg cct atc tcc cca ctc tgg gcc atc ctc ttc	1389
Glu Ala Val Thr Gln Leu Pro Ile Ser Pro Leu Trp Ala Ile Leu Phe	
370 375 380 385	
ttc tcc atg ctg ttg atg ctg ggc att gac agc cag ttc tgc act gtg	1437
Phe Ser Met Leu Leu Met Leu Gly Ile Asp Ser Gln Phe Cys Thr Val	
390 395 400	
gag ggc ttc atc aca gcc ctg gtg gat gag tac ccc agg ctc ctc cgc	1485
Glu Gly Phe Ile Thr Ala Leu Val Asp Glu Tyr Pro Arg Leu Leu Arg	
405 410 415	
aac cgc aga gag ctc ttc att gct gct gtc tgc atc atc tcc tac ctg	1533
Asn Arg Arg Glu Leu Phe Ile Ala Ala Val Cys Ile Ile Ser Tyr Leu	
420 425 430	

atc ggt ctc tct aac atc act cag ggg ggt att tat gtc ttc aaa ctc 1581
 Ile Gly Leu Ser Asn Ile Thr Gln Gly Gly Ile Tyr Val Phe Lys Leu
 435 440 445
 ttt gac tac tac tct gcc agt ggc atg agc ctg ctg ttc ctc gtg ttc 1629
 Phe Asp Tyr Tyr Ser Ala Ser Gly Met Ser Leu Leu Phe Leu Val Phe
 450 455 460 465
 ttt gaa tgt gtc tct att tcc tgg ttt tac ggt gtc aac cga ttc tat 1677
 Phe Glu Cys Val Ser Ile Ser Trp Phe Tyr Gly Val Asn Arg Phe Tyr
 470 475 480
 gac aat atc caa gag atg gtt gga tcc agg ccc tgc atc tgg tgg aaa 1725
 Asp Asn Ile Gln Glu Met Val Gly Ser Arg Pro Cys Ile Trp Trp Lys
 485 490 495
 ctc tgc tgg tct ttc ttc aca cca atc att gtg gcg ggc gtg ttc att 1773
 Leu Cys Trp Ser Phe Phe Thr Pro Ile Ile Val Ala Gly Val Phe Ile
 500 505 510
 ttc agt gct gtg cag atg acg cca ctc acc atg gga aac tat gtt ttc 1821
 Phe Ser Ala Val Gln Met Thr Pro Leu Thr Met Gly Asn Tyr Val Phe
 515 520 525
 ccc aag tgg ggc cag ggt gtg ggc tgg ctg atg gct ctg tct tcc atg 1869
 Pro Lys Trp Gly Gln Gly Val Gly Trp Leu Met Ala Leu Ser Ser Met
 530 535 540 545
 gtc ctc atc ccc ggg tac atg gcc tac atg ttc ctc gcc cta aag ggc 1917
 Val Leu Ile Pro Gly Tyr Met Ala Tyr Met Phe Leu Ala Leu Lys Gly
 550 555 560
 tcc ctg aag cag cgc atc caa gtc atg gtc cag ccc agc gaa gac act 1965
 Ser Leu Lys Gln Arg Ile Gln Val Met Val Gln Pro Ser Glu Asp Thr
 565 570 575
 gtt cgc cca gag aat ggt cct gag cac gcc cag gcg ggc agc tcc acc 2013
 Val Arg Pro Glu Asn Gly Pro Glu His Ala Gln Ala Gly Ser Ser Thr
 580 585 590
 agc aag gag gcc tac atc tag ggtgggggcc actcaccgac ccgacactct 2064
 Ser Lys Glu Ala Tyr Ile *
 595
 cccccccga cctggctgag tgcgaccacc acttgatgtc tgaggatacc ttccatctca 2124
 acctacctcg agtgggtgatc cagacaccat caccacgcag agaggggagg tgggaggaca 2184
 gttagacccc tgggtgggcc ctgccgtggg caaggataacc cggtggcttc tggcactggc 2244
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<211> 599

<212> PRT

<213> Homo Sapiens

<400> 5

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 Lys Val Gln Lys Lys Ala Ala Asp Leu Pro Asp Arg Asp Thr Trp Lys
 35 40 45
 Gly Arg Phe Asp Phe Leu Met Ser Cys Val Gly Tyr Ala Ile Gly Leu
 50 55 60
 Gly Asn Val Trp Arg Phe Pro Tyr Leu Cys Gly Lys Asn Gly Gly Gly
 65 70 75 80
 Ala Phe Leu Ile Pro Tyr Phe Leu Thr Leu Ile Phe Ala Gly Val Pro
 85 90 95
 Leu Phe Leu Leu Glu Cys Ser Leu Gly Gln Tyr Thr Ser Ile Gly Gly
 100 105 110

Leu Gly Val Trp Lys Leu Ala Pro Met Phe Lys Gly Val Gly Leu Ala
 115 120 125
 Ala Ala Val Leu Ser Phe Trp Leu Asn Ile Tyr Tyr Ile Val Ile Ile
 130 135 140
 Ser Trp Ala Ile Tyr Tyr Leu Tyr Asn Ser Phe Thr Thr Thr Leu Pro
 145 150 155 160
 Trp Lys Gln Cys Asp Asn Pro Trp Asn Thr Asp Arg Cys Phe Ser Asn
 165 170 175
 Tyr Ser Met Val Asn Thr Thr Asn Met Thr Ser Ala Val Val Glu Phe
 180 185 190
 Trp Glu Arg Asn Met His Gln Met Thr Asp Gly Leu Asp Lys Pro Gly
 195 200 205
 Gln Ile Arg Trp Pro Leu Ala Ile Thr Leu Ala Ile Ala Trp Ile Leu
 210 215 220
 Val Tyr Phe Cys Ile Trp Lys Gly Val Gly Trp Thr Gly Lys Val Val
 225 230 235 240
 Tyr Phe Ser Ala Thr Tyr Pro Tyr Ile Met Leu Ile Ile Leu Phe Phe
 245 250 255
 Arg Gly Val Thr Leu Pro Gly Ala Lys Glu Gly Ile Leu Phe Tyr Ile
 260 265 270
 Thr Pro Asn Phe Arg Lys Leu Ser Asp Ser Glu Val Trp Leu Asp Ala
 275 280 285
 Ala Thr Gln Ile Phe Phe Ser Tyr Gly Leu Gly Leu Gly Ser Leu Ile
 290 295 300
 Ala Leu Gly Ser Tyr Asn Ser Phe His Asn Asn Val Tyr Arg Asp Ser
 305 310 315 320
 Ile Ile Val Cys Cys Ile Asn Ser Cys Thr Ser Met Phe Ala Gly Phe
 325 330 335
 Val Ile Phe Ser Ile Val Gly Phe Met Ala His Val Thr Lys Arg Ser
 340 345 350
 Ile Ala Asp Val Ala Ala Ser Gly Pro Gly Leu Ala Phe Leu Ala Tyr
 355 360 365
 Pro Glu Ala Val Thr Gln Leu Pro Ile Ser Pro Leu Trp Ala Ile Leu
 370 375 380
 Phe Phe Ser Met Leu Leu Met Leu Gly Ile Asp Ser Gln Phe Cys Thr
 385 390 395 400
 Val Glu Gly Phe Ile Thr Ala Leu Val Asp Glu Tyr Pro Arg Leu Leu
 405 410 415
 Arg Asn Arg Arg Glu Leu Phe Ile Ala Ala Val Cys Ile Ile Ser Tyr
 420 425 430
 Leu Ile Gly Leu Ser Asn Ile Thr Gln Gly Gly Ile Tyr Val Phe Lys
 435 440 445
 Leu Phe Asp Tyr Tyr Ser Ala Ser Gly Met Ser Leu Leu Phe Leu Val
 450 455 460
 Phe Phe Glu Cys Val Ser Ile Ser Trp Phe Tyr Gly Val Asn Arg Phe
 465 470 475 480
 Tyr Asp Asn Ile Gln Glu Met Val Gly Ser Arg Pro Cys Ile Trp Trp
 485 490 495
 Lys Leu Cys Trp Ser Phe Phe Thr Pro Ile Ile Val Ala Gly Val Phe
 500 505 510
 Ile Phe Ser Ala Val Gln Met Thr Pro Leu Thr Met Gly Asn Tyr Val
 515 520 525
 Phe Pro Lys Trp Gly Gln Gly Val Gly Trp Leu Met Ala Leu Ser Ser
 530 535 540
 Met Val Leu Ile Pro Gly Tyr Met Ala Tyr Met Phe Leu Ala Leu Lys
 545 550 555 560
 Gly Ser Leu Lys Gln Arg Ile Gln Val Met Val Gln Pro Ser Glu Asp
 565 570 575
 Thr Val Arg Pro Glu Asn Gly Pro Glu His Ala Gln Ala Gly Ser Ser
 580 585 590
 Thr Ser Lys Glu Ala Tyr Ile
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<210> 6
 <211> 1800
 <212> DNA
 <213> Homo Sapiens

<220>

<221> CDS

<222> (1)...(1800)

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1 5 10 15	
gtc agc gag gcc cct gtg gcc aat gac aag ccc aaa acc ttg gtg gtc	96
Val Ser Glu Ala Pro Val Ala Asn Asp Lys Pro Lys Thr Leu Val Val	
20 25 30	
aag gtg cag aag aag gcg gca gac ctc ccc gac cgg gac acg tgg aag	144
Lys Val Gln Lys Lys Ala Ala Asp Leu Pro Asp Arg Asp Thr Trp Lys	
35 40 45	
ggc cgc ttc gac ttc ctc atg tcc tgt gtg ggc tat gcc atc ggc ctg	192
Gly Arg Phe Asp Phe Leu Met Ser Cys Val Gly Tyr Ala Ile Gly Leu	
50 55 60	
ggc aac gtc tgg agg ttc ccc tat ctc tgc ggg aaa aat ggt ggg gga	240
Gly Asn Val Trp Arg Phe Pro Tyr Leu Cys Gly Lys Asn Gly Gly Gly	
65 70 75 80	
gcc ttc ctg atc ccc tat ttc ctg aca ctc atc ttt gcg ggg gtc cca	288
Ala Phe Leu Ile Pro Tyr Phe Leu Thr Leu Ile Phe Ala Gly Val Pro	
85 90 95	
ctc ttc ctg ctg gag tgc tcc ctg ggc cag tac acc tcc atc ggg ggg	336
Leu Phe Leu Leu Glu Cys Ser Leu Gly Gln Tyr Thr Ser Ile Gly Gly	
100 105 110	
cta ggg gta tgg aag ctg gct cct atg ttc aag ggc gtg ggc ctt gcg	384
Leu Gly Val Trp Lys Leu Ala Pro Met Phe Lys Gly Val Gly Leu Ala	
115 120 125	
gct gct gtg cta tca ttc tgg ctg aac atc tac tac atc gtc atc atc	432
Ala Ala Val Leu Ser Phe Trp Leu Asn Ile Tyr Tyr Ile Val Ile Ile	
130 135 140	
tcc tgg gcc att tac tac ctg tac aac tcc ttc acc acg aca ctg ccg	480
Ser Trp Ala Ile Tyr Tyr Leu Tyr Asn Ser Phe Thr Thr Thr Leu Pro	
145 150 155 160	
tgg aaa cag tgc gac aac ccc tgg aac aca gac cgc tgc ttc tcc aac	528
Trp Lys Gln Cys Asp Asn Pro Trp Asn Thr Asp Arg Cys Phe Ser Asn	
165 170 175	
tac agc atg gtc aac act acc aac atg acc agc gct gtg gtg gag ttc	576
Tyr Ser Met Val Asn Thr Thr Asn Met Thr Ser Ala Val Val Glu Phe	
180 185 190	
tgg gag cgc aac atg cat cag atg acg gac ggg ctg gat aag cca ggt	624
Trp Glu Arg Asn Met His Gln Met Thr Asp Gly Leu Asp Lys Pro Gly	
195 200 205	
cag atc cgc tgg cca ctg gcc atc acg ctg gcc atc gcc tgg atc ctt	672
Gln Ile Arg Trp Pro Leu Ala Ile Thr Leu Ala Ile Ala Trp Ile Leu	
210 215 220	
gtg tat ttc tgt atc tgg aag ggt gtt ggc tgg act gga aag gtg gtc	720
Val Tyr Phe Cys Ile Trp Lys Gly Val Gly Trp Thr Gly Lys Val Val	
225 230 235 240	
tac ttt tca gcc aca tac ccc tac atc atg ctg atc atc ctg ttc ttc	768
Tyr Phe Ser Ala Thr Tyr Pro Tyr Ile Met Leu Ile Ile Leu Phe Phe	
245 250 255	

cgt gga gtg acg ctg ccc ggg gcc aag gag ggc atc ctc ttc tac atc	816
Arg Gly Val Thr Leu Pro Gly Ala Lys Glu Gly Ile Leu Phe Tyr Ile	
260 265 270	
aca ccc aac ttc cgc aag ctg tct gac tcc gag gtg tgg ctg gat gcg	864
Thr Pro Asn Phe Arg Lys Leu Ser Asp Ser Glu Val Trp Leu Asp Ala	
275 280 285	
gca acc cag atc ttc ttc tca tac ggg ctg ggc ctg ggg tcc ctg atc	912
Ala Thr Gln Ile Phe Phe Ser Tyr Gly Leu Gly Leu Gly Ser Leu Ile	
290 295 300	
gct ctc ggg agc tac aac tct ttc cac aac aat gtc tac agg gac tcc	960
Ala Leu Gly Ser Tyr Asn Ser Phe His Asn Asn Val Tyr Arg Asp Ser	
305 310 315 320	
atc atc gtc tgc tgc atc aat tcg tgc acc agc atg ttc gca gga ttc	1008
Ile Ile Val Cys Cys Ile Asn Ser Cys Thr Ser Met Phe Ala Gly Phe	
325 330 335	
gtc atc ttc tcc atc gtg ggc ttc atg gcc cat gtc acc aag agg tcc	1056
Val Ile Phe Ser Ile Val Gly Phe Met Ala His Val Thr Lys Arg Ser	
340 345 350	
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Ile Ala Asp Val Ala Ala Ser Gly Pro Gly Leu Ala Phe Leu Ala Tyr	
355 360 365	
cca gag gcg gtg acc cag ctg cct atc tcc cca ctc tgg gcc atc ctc	1152
Pro Glu Ala Val Thr Gln Leu Pro Ile Ser Pro Leu Trp Ala Ile Leu	
370 375 380	
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Phe Phe Ser Met Leu Leu Met Leu Gly Ile Asp Ser Gln Phe Cys Thr	
385 390 395 400	
gtg gag ggc ttc atc aca gcc ctg gtg gat gag tac ccc agg ctc ctc	1248
Val Glu Gly Phe Ile Thr Ala Leu Val Asp Glu Tyr Pro Arg Leu Leu	
405 410 415	
cgc aac cgc aga gag ctc ttc att gct gct gtc tgc atc atc tcc tac	1296
Arg Asn Arg Arg Glu Leu Phe Ile Ala Ala Val Cys Ile Ile Ser Tyr	
420 425 430	
ctg atc ggt ctc tct aac atc act cag ggg ggt att tat gtc ttc aaa	1344
Leu Ile Gly Leu Ser Asn Ile Thr Gln Gly Gly Ile Tyr Val Phe Lys	
435 440 445	
ctc ttt gac tac tac tct gcc agt ggc atg agc ctg ctg ttc ctc gtg	1392
Leu Phe Asp Tyr Tyr Ser Ala Ser Gly Met Ser Leu Leu Phe Leu Val	
450 455 460	
ttc ttt gaa tgt gtc tct att tcc tgg ttt tac ggt gtc aac cga ttc	1440
Phe Phe Glu Cys Val Ser Ile Ser Trp Phe Tyr Gly Val Asn Arg Phe	
465 470 475 480	
tat gac aat atc caa gag atg gtt gga tcc agg ccc tgc atc tgg tgg	1488
Tyr Asp Asn Ile Gln Glu Met Val Gly Ser Arg Pro Cys Ile Trp Trp	
485 490 495	
aaa ctc tgc tgg tct ttc ttc aca cca atc att gtg gcg ggc gtg ttc	1536
Lys Leu Cys Trp Ser Phe Phe Thr Pro Ile Ile Val Ala Gly Val Phe	
500 505 510	
att ttc agt gct gtg cag atg acg cca ctc acc atg gga aac tat gtt	1584
Ile Phe Ser Ala Val Gln Met Thr Pro Leu Thr Met Gly Asn Tyr Val	
515 520 525	
ttc ccc aag tgg ggc cag ggt gtg ggc tgg ctg atg gct ctg tct tcc	1632

Phe Pro Lys Trp Gly Gln Gly Val Gly Trp Leu Met Ala Leu Ser Ser
 530 535 540
 atg gtc ctc atc ccc ggg tac atg gcc tac atg ttc ctc gcc cta aag 1680
 Met Val Leu Ile Pro Gly Tyr Met Ala Tyr Met Phe Leu Ala Leu Lys
 545 550 555 560
 ggc tcc ctg aag cag cgc atc caa gtc atg gtc cag ccc agc gaa gac 1728
 Gly Ser Leu Lys Gln Arg Ile Gln Val Met Val Gln Pro Ser Glu Asp
 565 570 575
 act gtt cgc cca gag aat ggt cct gag cac gcc cag gcg ggc agc tcc 1776
 Thr Val Arg Pro Glu Asn Gly Pro Glu His Ala Gln Ala Gly Ser Ser
 580 585 590
 acc agc aag gag gcc tac atc tag 1800
 Thr Ser Lys Glu Ala Tyr Ile *
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 <212> DNA
 <213> Homo Sapiens

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 <221> CDS
 <222> (85)...(1188)

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 Met Asp Asp Ala Ala Val Leu Lys Arg
 1 5

 cga ggc tac ctc ctg ggg ata aat tta gga gag ggc tcc tat gca aaa 159
 Arg Gly Tyr Leu Leu Gly Ile Asn Leu Gly Glu Gly Ser Tyr Ala Lys
 10 15 20 25
 gta aaa tct gct tac tct gag cgc ctg aag ttc aat gtg gcg atc aag 207
 Val Lys Ser Ala Tyr Ser Glu Arg Leu Lys Phe Asn Val Ala Ile Lys
 30 35 40
 atc atc gac cgc aag aag gcc ccc gca gac ttc ttg gag aaa ttc ctt 255
 Ile Ile Asp Arg Lys Lys Ala Pro Ala Asp Phe Leu Glu Lys Phe Leu
 45 50 55
 ccc cgg gaa att gag att ctg gcc atg tta aac cac tgc tcc atc att 303
 Pro Arg Glu Ile Glu Ile Leu Ala Met Leu Asn His Cys Ser Ile Ile
 60 65 70
 aag acc tac gag atc ttt gag aca tca cat ggc aag gtc tac atc gtc 351
 Lys Thr Tyr Glu Ile Phe Glu Thr Ser His Gly Lys Val Tyr Ile Val
 75 80 85
 atg gag ctc gcg gtc cag ggc gac ctc ctc gag tta atc aaa acc cgg 399
 Met Glu Leu Ala Val Gln Gly Asp Leu Leu Glu Leu Ile Lys Thr Arg
 90 95 100 105
 gga gcc ctg cat gag gac gaa gct cgc aag aag ttc cac cag ctt tcc 447
 Gly Ala Leu His Glu Asp Glu Ala Arg Lys Lys Phe His Gln Leu Ser
 110 115 120
 ttg gcc atc aag tac tgc cac gac ctg gac gtc gtc cac cgg gac ctc 495
 Leu Ala Ile Lys Tyr Cys His Asp Leu Asp Val Val His Arg Asp Leu
 125 130 135
 aag tgt gac aac ctt ctc ctt gac aag gac ttc aac atc aag ctg tcc 543
 Lys Cys Asp Asn Leu Leu Leu Asp Lys Asp Phe Asn Ile Lys Leu Ser

140	145	150	
gac ttc agc ttc tcc aag cgc tgc ctg cgg gat	gac agt ggt cga atg	591	
Asp Phe Ser Phe Ser Lys Arg Cys Leu Arg Asp	Asp Ser Gly Arg Met		
155	160	165	
gcc tta agc aag acc ttc tgt ggg tca cca gcg tat gcg gcc cca gag	639		
Ala Leu Ser Lys Thr Phe Cys Gly Ser Pro Ala Tyr Ala Ala Pro Glu			
170	175	180	
gtg ctg cag ggc att ccc tac cag ccc aag gtg tac gac atc tgg agc	687		
Val Leu Gln Gly Ile Pro Tyr Gln Pro Lys Val Tyr Asp Ile Trp Ser			
	190	200	
cta ggc gtg atc ctc tac atc atg gtc tgc ggc tcc atg ccc tac gac	735		
Leu Gly Val Ile Leu Tyr Ile Met Val Cys Gly Ser Met Pro Tyr Asp			
	205	215	
gac tcc aac atc aag aag atg ctg cgt atc cag aag gag cac cgc gtc	783		
Asp Ser Asn Ile Lys Lys Met Leu Arg Ile Gln Lys Glu His Arg Val			
	220	230	
aac ttc cca cgc tcc aag cac ctg aca ggc gag tgc aag gac ctc atc	831		
Asn Phe Pro Arg Ser Lys His Leu Thr Gly Glu Cys Lys Asp Leu Ile			
	235	245	
tac cac atg ctg cag ccc gac gtc aac cgg cgg ctc cac atc gac gag	879		
Tyr His Met Leu Gln Pro Asp Val Asn Arg Arg Leu His Ile Asp Glu			
	255	260	
atc ctc agc cac tgc tgg atg cag ccc aag gca cgg gga tct ccc tct	927		
Ile Leu Ser His Cys Trp Met Gln Pro Lys Ala Arg Gly Ser Pro Ser			
	270	275	
gtg gcc atc aac aag gag ggg gag agt tcc cgg gga act gaa ccc ttg	975		
Val Ala Ile Asn Lys Glu Gly Glu Ser Ser Arg Gly Thr Glu Pro Leu			
	285	290	
tgg acc ccc gaa cct ggc tct gac aag aag tct gcc acc aag ctg gag	1023		
Trp Thr Pro Glu Pro Gly Ser Asp Lys Lys Ser Ala Thr Lys Leu Glu			
	300	310	
cct gag gga gag gca cag ccc cag gca cag cct gag aca aaa ccc gag	1071		
Pro Glu Gly Glu Ala Gln Pro Gln Ala Gln Pro Glu Thr Lys Pro Glu			
	315	320	
ggg aca gca atg caa atg tcc agg cag tcg gag atc ctg ggt ttc ccc	1119		
Gly Thr Ala Met Gln Met Ser Arg Gln Ser Glu Ile Leu Gly Phe Pro			
	330	335	
agc aag ccg tcg act atg gag aca gag gaa ggg ccc ccc caa cag cct	1167		
Ser Lys Pro Ser Thr Met Glu Thr Glu Glu Gly Pro Pro Gln Gln Pro			
	350	355	
cca gag acg cgg gcc cag tga gcttcttgcg gccagggaa tgagatggag	1218		
Pro Glu Thr Arg Ala Gln *			
	365		
ctcacggcctt aaagcccaag ctctgaagaa gtcaagggtg gagccagaga aggaaggcag	1278		
ccccagatga gcctctatatt tcatcagctt cttctctctc cccttgaact tggttaacca	1338		
catggttctc ccgtggcccc taggtggatg aggccaaagt caaatccaag gctgagacag	1398		
tcgtgcgact cctactcccc cagagcgtga cccggagcag gtgctggaca cagagcctgt	1458		
ctcagcagag ggtccccact ggcgcgaacg gctcagtgac agcaagagca ggaagagcag	1518		
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<211> 367

<212> PRT

<213> Homo Sapiens

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20     25     30
Arg Leu Lys Phe Asn Val Ala Ile Lys Ile Ile Asp Arg Lys Lys Ala
35     40     45
Pro Ala Asp Phe Leu Glu Lys Phe Leu Pro Arg Glu Ile Glu Ile Leu
50     55     60
Ala Met Leu Asn His Cys Ser Ile Ile Lys Thr Tyr Glu Ile Phe Glu
65     70     75
Thr Ser His Gly Lys Val Tyr Ile Val Met Glu Leu Ala Val Gln Gly
85     90     95
Asp Leu Leu Glu Leu Ile Lys Thr Arg Gly Ala Leu His Glu Asp Glu
100    105    110
Ala Arg Lys Lys Phe His Gln Leu Ser Leu Ala Ile Lys Tyr Cys His
115    120    125
Asp Leu Asp Val Val His Arg Asp Leu Lys Cys Asp Asn Leu Leu Leu
130    135    140
Asp Lys Asp Phe Asn Ile Lys Leu Ser Asp Phe Ser Phe Ser Lys Arg
145    150    155
Cys Leu Arg Asp Asp Ser Gly Arg Met Ala Leu Ser Lys Thr Phe Cys
165    170    175
Gly Ser Pro Ala Tyr Ala Ala Pro Glu Val Leu Gln Gly Ile Pro Tyr
180    185    190
Gln Pro Lys Val Tyr Asp Ile Trp Ser Leu Gly Val Ile Leu Tyr Ile
195    200    205
Met Val Cys Gly Ser Met Pro Tyr Asp Asp Ser Asn Ile Lys Lys Met
210    215    220
Leu Arg Ile Gln Lys Glu His Arg Val Asn Phe Pro Arg Ser Lys His
225    230    235
Leu Thr Gly Glu Cys Lys Asp Leu Ile Tyr His Met Leu Gln Pro Asp
245    250    255
Val Asn Arg Arg Leu His Ile Asp Glu Ile Leu Ser His Cys Trp Met
260    265    270
Gln Pro Lys Ala Arg Gly Ser Pro Ser Val Ala Ile Asn Lys Glu Gly
275    280    285
Glu Ser Ser Arg Gly Thr Glu Pro Leu Trp Thr Pro Glu Pro Gly Ser
290    295    300
Asp Lys Lys Ser Ala Thr Lys Leu Glu Pro Glu Gly Glu Ala Gln Pro
305    310    315
Gln Ala Gln Pro Glu Thr Lys Pro Glu Gly Thr Ala Met Gln Met Ser
325    330    335
Arg Gln Ser Glu Ile Leu Gly Phe Pro Ser Lys Pro Ser Thr Met Glu
340    345    350
Thr Glu Glu Gly Pro Pro Gln Gln Pro Pro Glu Thr Arg Ala Gln
355    360    365

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<210> 9
<211> 1104
<212> DNA
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<220>
<221> CDS
<222> (1)...(1104)

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Met Asp Asp Ala Ala Val Leu Lys Arg Arg Gly Tyr Leu Leu Gly Ile
1      5      10      15

aat tta gga gag ggc tcc tat gca aaa gta aaa tct gct tac tct gag 96
Asn Leu Gly Glu Gly Ser Tyr Ala Lys Val Lys Ser Ala Tyr Ser Glu
20     25     30

cgc ctg aag ttc aat gtg gcg atc aag atc atc gac cgc aag aag gcc 144

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Arg	Leu	Lys	Phe	Asn	Val	Ala	Ile	Lys	Ile	Ile	Asp	Arg	Lys	Lys	Ala	
		35					40					45				
ccc	gca	gac	ttc	ttg	gag	aaa	ttc	ctt	ccc	cgg	gaa	att	gag	att	ctg	192
Pro	Ala	Asp	Phe	Leu	Glu	Lys	Phe	Leu	Pro	Arg	Glu	Ile	Glu	Ile	Leu	
	50					55					60					
gcc	atg	tta	aac	cac	tgc	tcc	atc	att	aag	acc	tac	gag	atc	ttt	gag	240
Ala	Met	Leu	Asn	His	Cys	Ser	Ile	Ile	Lys	Thr	Tyr	Glu	Ile	Phe	Glu	
	65				70				75						80	
aca	tca	cat	ggc	aag	gtc	tac	atc	gtc	atg	gag	ctc	gcg	gtc	cag	ggc	288
Thr	Ser	His	Gly	Lys	Val	Tyr	Ile	Val	Met	Glu	Leu	Ala	Val	Gln	Gly	
				85					90					95		
gac	ctc	ctc	gag	tta	atc	aaa	acc	cgg	gga	gcc	ctg	cat	gag	gac	gaa	336
Asp	Leu	Leu	Glu	Leu	Ile	Lys	Thr	Arg	Gly	Ala	Leu	His	Glu	Asp	Glu	
			100					105					110			
gct	cgc	aag	aag	ttc	cac	cag	ctt	tcc	ttg	gcc	atc	aag	tac	tgc	cac	384
Ala	Arg	Lys	Lys	Phe	His	Gln	Leu	Ser	Leu	Ala	Ile	Lys	Tyr	Cys	His	
		115					120					125				
gac	ctg	gac	gtc	gtc	cac	cgg	gac	ctc	aag	tgt	gac	aac	ctt	ctc	ctt	432
Asp	Leu	Asp	Val	Val	His	Arg	Asp	Leu	Lys	Cys	Asp	Asn	Leu	Leu	Leu	
	130					135					140					
gac	aag	gac	ttc	aac	atc	aag	ctg	tcc	gac	ttc	agc	ttc	tcc	aag	cgc	480
Asp	Lys	Asp	Phe	Asn	Ile	Lys	Leu	Ser	Asp	Phe	Ser	Phe	Ser	Lys	Arg	
	145				150				155						160	
tgc	ctg	cgg	gat	gac	agt	ggc	cga	atg	gcc	tta	agc	aag	acc	ttc	tgt	528
Cys	Leu	Arg	Asp	Asp	Ser	Gly	Arg	Met	Ala	Leu	Ser	Lys	Thr	Phe	Cys	
				165				170						175		
ggg	tca	cca	gcg	tat	gcg	gcc	cca	gag	gtg	ctg	cag	ggc	att	ccc	tac	576
Gly	Ser	Pro	Ala	Tyr	Ala	Ala	Pro	Glu	Val	Leu	Gln	Gly	Ile	Pro	Tyr	
			180					185					190			
cag	ccc	aag	gtg	tac	gac	atc	tgg	agc	cta	ggc	gtg	atc	ctc	tac	atc	624
Gln	Pro	Lys	Val	Tyr	Asp	Ile	Trp	Ser	Leu	Gly	Val	Ile	Leu	Tyr	Ile	
		195					200					205				
atg	gtc	tgc	ggc	tcc	atg	ccc	tac	gac	gac	tcc	aac	atc	aag	aag	atg	672
Met	Val	Cys	Gly	Ser	Met	Pro	Tyr	Asp	Asp	Ser	Asn	Ile	Lys	Lys	Met	
	210					215					220					
ctg	cgt	atc	cag	aag	gag	cac	cgc	gtc	aac	ttc	cca	cgc	tcc	aag	cac	720
Leu	Arg	Ile	Gln	Lys	Glu	His	Arg	Val	Asn	Phe	Pro	Arg	Ser	Lys	His	
	225				230				235						240	
ctg	aca	ggc	gag	tgc	aag	gac	ctc	atc	tac	cac	atg	ctg	cag	ccc	gac	768
Leu	Thr	Gly	Glu	Cys	Lys	Asp	Leu	Ile	Tyr	His	Met	Leu	Gln	Pro	Asp	
				245				250						255		
gtc	aac	cgg	cgg	ctc	cac	atc	gac	gag	atc	ctc	agc	cac	tgc	tgg	atg	816
Val	Asn	Arg	Arg	Leu	His	Ile	Asp	Glu	Ile	Leu	Ser	His	Cys	Trp	Met	
				260				265					270			
cag	ccc	aag	gca	cgg	gga	tct	ccc	tct	gtg	gcc	atc	aac	aag	gag	ggg	864
Gln	Pro	Lys	Ala	Arg	Gly	Ser	Pro	Ser	Val	Ala	Ile	Asn	Lys	Glu	Gly	
		275					280					285				
gag	agt	tcc	cgg	gga	act	gaa	ccc	ttg	tgg	acc	ccc	gaa	cct	ggc	tct	912
Glu	Ser	Ser	Arg	Gly	Thr	Glu	Pro	Leu	Trp	Thr	Pro	Glu	Pro	Gly	Ser	
	290					295					300					
gac	aag	aag	tct	gcc	acc	aag	ctg	gag	cct	gag	gga	gag	gca	cag	ccc	960
Asp	Lys	Lys	Ser	Ala	Thr	Lys	Leu	Glu	Pro	Glu	Gly	Glu	Ala	Gln	Pro	

305	310	315	320	
cag gca cag cct gag aca aaa ccc gag ggg aca gca atg caa atg tcc				1008
Gln Ala Gln Pro Glu Thr Lys Pro Glu Gly Thr Ala Met Gln Met Ser				
	325	330	335	
agg cag tcg gag atc ctg ggt ttc ccc agc aag ccg tcg act atg gag				1056
Arg Gln Ser Glu Ile Leu Gly Phe Pro Ser Lys Pro Ser Thr Met Glu				
	340	345	350	
aca gag gaa ggg ccc ccc caa cag cct cca gag acg cgg gcc cag tga				1104
Thr Glu Glu Gly Pro Pro Gln Gln Pro Pro Glu Thr Arg Ala Gln *				
	355	360	365	
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Met Val Arg Arg Leu Ala Arg Gly Cys Trp Ser Ala Leu Trp Asp Tyr				
1	5	10	15	
gag acg ccc aag gtg atc gtg gtg agg aac cgg cgc ctg ggg gtc ctg				96
Glu Thr Pro Lys Val Ile Val Val Arg Asn Arg Arg Leu Gly Val Leu				
	20	25	30	
tac cgc gcc gtg cag ctg ctc atc ctg ctc tac ttc gtg tgg tac gta				144
Tyr Arg Ala Val Gln Leu Leu Ile Leu Leu Tyr Phe Val Trp Tyr Val				
	35	40	45	
ttc atc gtg cag aaa agc tac cag gag agc gag acg ggc ccc gag agc				192
Phe Ile Val Gln Lys Ser Tyr Gln Glu Ser Glu Thr Gly Pro Glu Ser				
	50	55	60	
tcc atc atc acc aag gtc aag ggg atc acc acg tcc gag cac aaa gtg				240
Ser Ile Ile Thr Lys Val Lys Gly Ile Thr Thr Ser Glu His Lys Val				
	65	70	75	80
tgg gac gtg gag gag tac gtg aag ccc ccc gag ggg ggc agc gtg ttc				288
Trp Asp Val Glu Glu Tyr Val Lys Pro Pro Glu Gly Gly Ser Val Phe				
	85	90	95	
agc atc atc acc agg gtc gag gcc acc cac tcc cag acc cag gga acc				336
Ser Ile Ile Thr Arg Val Glu Ala Thr His Ser Gln Thr Gln Gly Thr				
	100	105	110	
tgc ccc gag agc ata agg gtc cac aac gcc acc tgc ctc tcc gac gcc				384
Cys Pro Glu Ser Ile Arg Val His Asn Ala Thr Cys Leu Ser Asp Ala				
	115	120	125	
gac tgc gtg gct ggg gag ctg gac atg ctg gga aac ggc ctg agg acc				432
Asp Cys Val Ala Gly Glu Leu Asp Met Leu Gly Asn Gly Leu Arg Thr				
	130	135	140	
ggg cgc tgt gtg ccc tat tac cag ggg ccc tcc aag acc tgc gag gtg				480
Gly Arg Cys Val Pro Tyr Gln Gly Pro Ser Lys Thr Cys Glu Val				
	145	150	155	160
ttc ggc tgg tgc ccg gtg gaa gat ggg gcc tct gtc agc caa ttt ctg				528
Phe Gly Trp Cys Pro Val Glu Asp Gly Ala Ser Val Ser Gln Phe Leu				
	165	170	175	

ggt acg atg gcc cca aat ttc acc atc ctc atc aag aac agc atc cac Gly Thr Met Ala Pro Asn Phe Thr Ile Leu Ile Lys Asn Ser Ile His 180 185 190	576
tac ccc aaa ttc cac ttc tcc aag ggc aac atc gcc gac cgc aca gac Tyr Pro Lys Phe His Phe Ser Lys Gly Asn Ile Ala Asp Arg Thr Asp 195 200 205	624
ggg tac ctg aag cgc tgc acg ttc cac gag gcc tcc gac ctc tac tgc Gly Tyr Leu Lys Arg Cys Thr Phe His Glu Ala Ser Asp Leu Tyr Cys 210 215 220	672
ccc atc ttc aag ctg ggc ttt atc gtg gag aag gct ggg gag agc ttc Pro Ile Phe Lys Leu Gly Phe Ile Val Glu Lys Ala Gly Glu Ser Phe 225 230 235 240	720
aca gag ctc gca cac aag ggt ggt gtc atc ggg gtc att atc aac tgg Thr Glu Leu Ala His Lys Gly Gly Val Ile Gly Val Ile Ile Asn Trp 245 250 255	768
gac tgt gac ctg gac ctg cct gca tgc gag tgc aac ccc aag tac tcc Asp Cys Asp Leu Asp Leu Pro Ala Ser Glu Cys Asn Pro Lys Tyr Ser 260 265 270	816
ttc cgg agg ctt gac ccc aag cac gtg cct gcc tgc tca ggc tac aac Phe Arg Arg Leu Asp Pro Lys His Val Pro Ala Ser Ser Gly Tyr Asn 275 280 285	864
ttc agg ttt gcc aaa tac tac aag atc aat ggc acc acc acc cgc acg Phe Arg Phe Ala Lys Tyr Tyr Lys Ile Asn Gly Thr Thr Thr Arg Thr 290 295 300	912
ctc atc aag gcc tac ggg atc cgc att gac gtc att gtg cat gga cag Leu Ile Lys Ala Tyr Gly Ile Arg Ile Asp Val Ile Val His Gly Gln 305 310 315 320	960
gcc ggg aag ttc agc ctg att ccc acc att att aat ctg gcc aca gct Ala Gly Lys Phe Ser Leu Ile Pro Thr Ile Ile Asn Leu Ala Thr Ala 325 330 335	1008
ctg act tcc gtc ggg gtg ggc tcc ttc ctg tgc gac tgg atc ttg cta Leu Thr Ser Val Gly Val Gly Ser Phe Leu Cys Asp Trp Ile Leu Leu 340 345 350	1056
aca ttc atg aac aaa aac aag gtc tac agc cat aag aaa ttt gac aag Thr Phe Met Asn Lys Asn Lys Val Tyr Ser His Lys Lys Phe Asp Lys 355 360 365	1104
gtg tgt acg ccg agc cac ccc tca ggt agc tgg cct gtg acc ctt gcc Val Cys Thr Pro Ser His Pro Ser Gly Ser Trp Pro Val Thr Leu Ala 370 375 380	1152
cgt gta ttg ggc cag gcc cct ccc gaa ccc ggc cac cgc tcc gag gac Arg Val Leu Gly Gln Ala Pro Pro Glu Pro Gly His Arg Ser Glu Asp 385 390 395 400	1200
cag cac ccc agc cct cca tca ggc cag gag ggc caa caa ggg gca gaa Gln His Pro Ser Pro Pro Ser Gly Gln Glu Gly Gln Gln Gly Ala Glu 405 410 415	1248
tgt ggc cca gcc ttc ccg ccc ctg cgg cct tgc ccc atc tct gcc cct Cys Gly Pro Ala Phe Pro Pro Leu Arg Pro Cys Pro Ile Ser Ala Pro 420 425 430	1296
tct gag cag atg gtg gac act cct gcc tcc gag cct gcc caa gcc tcc Ser Glu Gln Met Val Asp Thr Pro Ala Ser Glu Pro Ala Gln Ala Ser 435 440 445	1344

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 450 455

1389

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 <212> PRT
 <213> Homo Sapiens

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 20 25 30
 Tyr Arg Ala Val Gln Leu Leu Ile Leu Leu Tyr Phe Val Trp Tyr Val
 35 40 45
 Phe Ile Val Gln Lys Ser Tyr Gln Glu Ser Glu Thr Gly Pro Glu Ser
 50 55 60
 Ser Ile Ile Thr Lys Val Lys Gly Ile Thr Thr Ser Glu His Lys Val
 65 70 75 80
 Trp Asp Val Glu Glu Tyr Val Lys Pro Pro Glu Gly Gly Ser Val Phe
 85 90 95
 Ser Ile Ile Thr Arg Val Glu Ala Thr His Ser Gln Thr Gln Gly Thr
 100 105 110
 Cys Pro Glu Ser Ile Arg Val His Asn Ala Thr Cys Leu Ser Asp Ala
 115 120 125
 Asp Cys Val Ala Gly Glu Leu Asp Met Leu Gly Asn Gly Leu Arg Thr
 130 135 140
 Gly Arg Cys Val Pro Tyr Tyr Gln Gly Pro Ser Lys Thr Cys Glu Val
 145 150 155 160
 Phe Gly Trp Cys Pro Val Glu Asp Gly Ala Ser Val Ser Gln Phe Leu
 165 170 175
 Gly Thr Met Ala Pro Asn Phe Thr Ile Leu Ile Lys Asn Ser Ile His
 180 185 190
 Tyr Pro Lys Phe His Phe Ser Lys Gly Asn Ile Ala Asp Arg Thr Asp
 195 200 205
 Gly Tyr Leu Lys Arg Cys Thr Phe His Glu Ala Ser Asp Leu Tyr Cys
 210 215 220
 Pro Ile Phe Lys Leu Gly Phe Ile Val Glu Lys Ala Gly Glu Ser Phe
 225 230 235 240
 Thr Glu Leu Ala His Lys Gly Gly Val Ile Gly Val Ile Ile Asn Trp
 245 250 255
 Asp Cys Asp Leu Asp Leu Pro Ala Ser Glu Cys Asn Pro Lys Tyr Ser
 260 265 270
 Phe Arg Arg Leu Asp Pro Lys His Val Pro Ala Ser Ser Gly Tyr Asn
 275 280 285
 Phe Arg Phe Ala Lys Tyr Tyr Lys Ile Asn Gly Thr Thr Thr Arg Thr
 290 295 300
 Leu Ile Lys Ala Tyr Gly Ile Arg Ile Asp Val Ile Val His Gly Gln
 305 310 315 320
 Ala Gly Lys Phe Ser Leu Ile Pro Thr Ile Ile Asn Leu Ala Thr Ala
 325 330 335
 Leu Thr Ser Val Gly Val Gly Ser Phe Leu Cys Asp Trp Ile Leu Leu
 340 345 350
 Thr Phe Met Asn Lys Asn Lys Val Tyr Ser His Lys Lys Phe Asp Lys
 355 360 365
 Val Cys Thr Pro Ser His Pro Ser Gly Ser Trp Pro Val Thr Leu Ala
 370 375 380
 Arg Val Leu Gly Gln Ala Pro Pro Glu Pro Gly His Arg Ser Glu Asp
 385 390 395 400
 Gln His Pro Ser Pro Pro Ser Gly Gln Glu Gly Gln Gln Gly Ala Glu
 405 410 415
 Cys Gly Pro Ala Phe Pro Pro Leu Arg Pro Cys Pro Ile Ser Ala Pro
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 435 440 445
 Thr Pro Thr Asp Pro Lys Gly Leu Ala Gln Leu
 450 455

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 <213> Homo Sapiens

<220>
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 gag acg ccc aag gtg atc gtg gtg agg aac cgg cgc ctg ggg gtc ctg 96
 Glu Thr Pro Lys Val Ile Val Val Arg Asn Arg Arg Leu Gly Val Leu
 20 25 30
 tac cgc gcc gtg cag ctg ctc atc ctg ctc tac ttc gtg tgg tac gta 144
 Tyr Arg Ala Val Gln Leu Leu Ile Leu Leu Tyr Phe Val Trp Tyr Val
 35 40 45
 ttc atc gtg cag aaa agc tac cag gag agc gag acg ggc ccc gag agc 192
 Phe Ile Val Gln Lys Ser Tyr Gln Glu Ser Glu Thr Gly Pro Glu Ser
 50 55 60
 tcc atc atc acc aag gtc aag ggg atc acc acg tcc gag cac aaa gtg 240
 Ser Ile Ile Thr Lys Val Lys Gly Ile Thr Thr Ser Glu His Lys Val
 65 70 75 80
 tgg gac gtg gag gag tac gtg aag ccc ccc gag ggg ggc agc gtg ttc 288
 Trp Asp Val Glu Glu Tyr Val Lys Pro Pro Glu Gly Gly Ser Val Phe
 85 90 95
 agc atc atc acc agg gtc gag gcc acc cac tcc cag acc cag gga acc 336
 Ser Ile Ile Thr Arg Val Glu Ala Thr His Ser Gln Thr Gln Gly Thr
 100 105 110
 tgc ccc gag agc ata agg gtc cac aac gcc acc tgc ctc tcc gac gcc 384
 Cys Pro Glu Ser Ile Arg Val His Asn Ala Thr Cys Leu Ser Asp Ala
 115 120 125
 gac tgc gtg gct ggg gag ctg gac atg ctg gga aac ggc ctg agg acc 432
 Asp Cys Val Ala Gly Glu Leu Asp Met Leu Gly Asn Gly Leu Arg Thr
 130 135 140
 ggg cgc tgt gtg ccc tat tac cag ggg ccc tcc aag acc tgc gag gtg 480
 Gly Arg Cys Val Pro Tyr Tyr Gln Gly Pro Ser Lys Thr Cys Glu Val
 145 150 155 160
 ttc ggc tgg tgc ccg gtg gaa gat ggg gcc tct gtc agc caa ttt ctg 528
 Phe Gly Trp Cys Pro Val Glu Asp Gly Ala Ser Val Ser Gln Phe Leu
 165 170 175
 ggt acg atg gcc cca aat ttc acc atc ctc atc aag aac agc atc cac 576
 Gly Thr Met Ala Pro Asn Phe Thr Ile Leu Ile Lys Asn Ser Ile His
 180 185 190
 tac ccc aaa ttc cac ttc tcc aag ggc aac atc gcc gac cgc aca gac 624
 Tyr Pro Lys Phe His Phe Ser Lys Gly Asn Ile Ala Asp Arg Thr Asp
 195 200 205
 ggg tac ctg aag cgc tgc acg ttc cac gag gcc tcc gac ctc tac tgc 672
 Gly Tyr Leu Lys Arg Cys Thr Phe His Glu Ala Ser Asp Leu Tyr Cys
 210 215 220
 ccc atc ttc aag ctg ggc ttt atc gtg gag aag gct ggg gag agc ttc 720

Pro	Ile	Phe	Lys	Leu	Gly	Phe	Ile	Val	Glu	Lys	Ala	Gly	Glu	Ser	Phe	
225					230					235					240	
aca	gag	ctc	gca	cac	aag	ggg	ggg	gtc	atc	ggg	gtc	att	atc	aac	tgg	768
Thr	Glu	Leu	Ala	His	Lys	Gly	Gly	Val	Ile	Gly	Val	Ile	Ile	Asn	Trp	
				245					250					255		
gac	tgt	gac	ctg	gac	ctg	cct	gca	tcg	gag	tgc	aac	ccc	aag	tac	tcc	816
Asp	Cys	Asp	Leu	Asp	Leu	Pro	Ala	Glu	Cys	Asn	Pro	Lys	Tyr	Ser		
				260				265					270			
ttc	cgg	agg	ctt	gac	ccc	aag	cac	gtg	cct	gcc	tcg	tca	ggc	tac	aac	864
Phe	Arg	Arg	Leu	Asp	Pro	Lys	His	Val	Pro	Ala	Ser	Ser	Gly	Tyr	Asn	
			275				280					285				
ttc	agg	ttt	gcc	aaa	tac	tac	aag	atc	aat	ggc	acc	acc	acc	cgc	acg	912
Phe	Arg	Phe	Ala	Lys	Tyr	Tyr	Lys	Ile	Asn	Gly	Thr	Thr	Thr	Arg	Thr	
	290					295					300					
ctc	atc	aag	gcc	tac	ggg	atc	cgc	att	gac	gtc	att	gtg	cat	gga	cag	960
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Ala	Gly	Lys	Phe	Ser	Leu	Ile	Pro	Thr	Ile	Ile	Asn	Leu	Ala	Thr	Ala	
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Val	Cys	Thr	Pro	Ser	His	Pro	Ser	Gly	Ser	Trp	Pro	Val	Thr	Leu	Ala	
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Gln	His	Pro	Ser	Pro	Pro	Ser	Gly	Gln	Glu	Gly	Gln	Gln	Gly	Ala	Glu	
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Cys	Gly	Pro	Ala	Phe	Pro	Pro	Leu	Arg	Pro	Cys	Pro	Ile	Ser	Ala	Pro	
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Ser	Glu	Gln	Met	Val	Asp	Thr	Pro	Ala	Ser	Glu	Pro	Ala	Gln	Ala	Ser	
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ccggcgcgcc gggacacgcg ggccggcttg gcg atg cac acc ctc act ggc ttc 354
                               Met His Thr Leu Thr Gly Phe
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Ser Leu Val Ser Leu Leu Ser Phe Gly Tyr Leu Ser Trp Asp Trp Ala
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Ser Ala Ala Pro Pro Gln Pro Pro His Ile Ile Phe Ile Leu Thr Asp
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gac caa ggc tac cac gac gtg ggc tac cat ggt tca gat atc gag acc 546
Asp Gln Gly Tyr His Asp Val Gly Tyr His Gly Ser Asp Ile Glu Thr
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cct acg ctg gac agg ctg gcg gcc aag ggg gtc aag ttg gag aat tat 594
Pro Thr Leu Asp Arg Leu Ala Ala Lys Gly Val Lys Leu Glu Asn Tyr
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tac atc cag ccc atc tgc acg cct tcg cgg agc cag ctc ctc act ggc 642
Tyr Ile Gln Pro Ile Cys Thr Pro Ser Arg Ser Gln Leu Leu Thr Gly
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agg tac cag atc cac aca gga ctc cag cat tcc atc atc cgc cca cag 690
Arg Tyr Gln Ile His Thr Gly Leu Gln His Ser Ile Ile Arg Pro Gln
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cag ccc aac tgc ctg ccc ctg gac cag gtg aca ctg cca cag aag ctg 738
Gln Pro Asn Cys Leu Pro Leu Asp Gln Val Thr Leu Pro Gln Lys Leu
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cag gag gca ggt tat tcc acc cat atg gtg ggc aag tgg cac ctg ggc 786
Gln Glu Ala Gly Tyr Ser Thr His Met Val Gly Lys Trp His Leu Gly
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ttc tac cgg aag gag tgt ctg ccc acc cgt cgg ggc ttc gac acc ttc 834
Phe Tyr Arg Lys Glu Cys Leu Pro Thr Arg Arg Gly Phe Asp Thr Phe
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ctg ggc tcg ctc acg ggc aat gtg gac tat tac acc tat gac aac tgt 882
Leu Gly Ser Leu Thr Gly Asn Val Asp Tyr Tyr Thr Tyr Asp Asn Cys
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gat ggc cca ggc gtg tgc ggc ttc gac ctg cac gag ggt gag aat gtg 930
Asp Gly Pro Gly Val Cys Gly Phe Asp Leu His Glu Gly Glu Asn Val
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gcc tgg ggg ctc agc ggc cag tac tcc act atg ctt tac gcc cag cgc 978
Ala Trp Gly Leu Ser Gly Gln Tyr Ser Thr Met Leu Tyr Ala Gln Arg
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gcc agc cat atc ctg gcc agc cac agc cct cag cgt ccc ctc ttc ctc 1026
Ala Ser His Ile Leu Ala Ser His Ser Pro Gln Arg Pro Leu Phe Leu
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tat gtg gcc ttc cag gca gta cac aca ccc ctg cag tcc cct cgt gag 1074
Tyr Val Ala Phe Gln Ala Val His Thr Pro Leu Gln Ser Pro Arg Glu
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gcg gcc atg gtg acc tgc atg gat gag gct gtg cgc aac atc acc tgg	1170
Ala Ala Met Val Thr Cys Met Asp Glu Ala Val Arg Asn Ile Thr Trp	
265 270 275	
gcc ctc aag cgc tac ggt ttc tac aac aac agt gtc atc atc ttc tcc	1218
Ala Leu Lys Arg Tyr Gly Phe Tyr Asn Asn Ser Val Ile Ile Phe Ser	
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agt gac aat ggt ggc cag act ttc tgc ggg ggc agc aac tgg ccg ctc	1266
Ser Asp Asn Gly Gly Gln Thr Phe Ser Gly Gly Ser Asn Trp Pro Leu	
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Arg Gly Arg Lys Gly Thr Tyr Trp Glu Gly Gly Val Arg Gly Leu Gly	
315 320 325	
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Phe Val His Ser Pro Leu Leu Lys Arg Lys Gln Arg Thr Ser Arg Ala	
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Leu Met His Ile Thr Asp Trp Tyr Pro Thr Leu Val Gly Leu Ala Gly	
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Gly Thr Thr Ser Ala Ala Asp Gly Leu Asp Gly Tyr Asp Val Trp Pro	
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Ala Ile Ser Glu Gly Arg Ala Ser Pro Arg Thr Glu Ile Leu His Asn	
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Ile Asp Pro Leu Tyr Asn His Ala Gln His Gly Ser Leu Glu Gly Gly	
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Phe Gly Ile Trp Asn Thr Ala Val Gln Ala Ala Ile Arg Val Gly Glu	
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Trp Lys Leu Leu Thr Gly Asp Pro Gly Tyr Gly Asp Trp Ile Pro Pro	
425 430 435	
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Gln Thr Leu Ala Thr Phe Pro Gly Ser Trp Trp Asn Leu Glu Arg Met	
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Ala Ser Val Arg Gln Ala Val Trp Leu Phe Asn Ile Ser Ala Asp Pro	
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tat gaa cgg gag gac ctg gct ggc cag cgg cct gat gtg gtc cgc acc	1794
Tyr Glu Arg Glu Asp Leu Ala Gly Gln Arg Pro Asp Val Val Arg Thr	
475 480 485	
ctg ctg gct cgc ctg gcc gaa tat aac cgc aca gcc atc ccg gta cgc	1842
Leu Leu Ala Arg Leu Ala Glu Tyr Asn Arg Thr Ala Ile Pro Val Arg	
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Tyr Pro Ala Glu Asn Pro Arg Ala His Pro Asp Phe Asn Gly Gly Ala	
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 Ala Arg Ser Phe Ser Arg Gly Arg Arg Lys Lys Lys Cys Lys Ile Cys
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 aag ctt cga tcc ttt ttc cgt aaa ctc aac acc agg cta atg tcc caa 2034
 Lys Leu Arg Ser Phe Phe Arg Lys Leu Asn Thr Arg Leu Met Ser Gln
 555 560 565

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 Arg Ile *

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 Ile Ile Phe Ile Leu Thr Asp Asp Gln Gly Tyr His Asp Val Gly Tyr
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 His Gly Ser Asp Ile Glu Thr Pro Thr Leu Asp Arg Leu Ala Ala Lys
 65 70 75 80
 Gly Val Lys Leu Glu Asn Tyr Tyr Ile Gln Pro Ile Cys Thr Pro Ser
 85 90 95
 Arg Ser Gln Leu Leu Thr Gly Arg Tyr Gln Ile His Thr Gly Leu Gln
 100 105 110
 His Ser Ile Ile Arg Pro Gln Gln Pro Asn Cys Leu Pro Leu Asp Gln
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 Arg Arg Gly Phe Asp Thr Phe Leu Gly Ser Leu Thr Gly Asn Val Asp
 165 170 175
 Tyr Tyr Thr Tyr Asp Asn Cys Asp Gly Pro Gly Val Cys Gly Phe Asp
 180 185 190
 Leu His Glu Gly Glu Asn Val Ala Trp Gly Leu Ser Gly Gln Tyr Ser
 195 200 205
 Thr Met Leu Tyr Ala Gln Arg Ala Ser His Ile Leu Ala Ser His Ser
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 Pro Gln Arg Pro Leu Phe Leu Tyr Val Ala Phe Gln Ala Val His Thr
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 Pro Leu Gln Ser Pro Arg Glu Tyr Leu Tyr Arg Tyr Arg Thr Met Gly

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Lys	Gln	Arg	Thr	Ser	Arg	Ala	Leu	Met	His	Ile	Thr	Asp	Trp	Tyr	Pro
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His	Gly	Ser	Leu	Glu	Gly	Gly	Phe	Gly	Ile	Trp	Asn	Thr	Ala	Val	Gln
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Ala	Ala	Ile	Arg	Val	Gly	Glu	Trp	Lys	Leu	Leu	Thr	Gly	Asp	Pro	Gly
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Glu	Glu	Glu	Glu	Gly	Arg	Ala	Arg	Ser	Phe	Ser	Arg	Gly	Arg	Arg	
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Tyr Leu Ser Trp Asp Trp Ala Lys Pro Ser Phe Val Ala Asp Gly Pro	
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Gly Glu Ala Gly Glu Gln Pro Ser Ala Ala Pro Pro Gln Pro Pro His	
35 40 45	
atc atc ttc atc ctc acg gac gac caa ggc tac cac gac gtg ggc tac	192
Ile Ile Phe Ile Leu Thr Asp Asp Gln Gly Tyr His Asp Val Gly Tyr	
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His Gly Ser Asp Ile Glu Thr Pro Thr Leu Asp Arg Leu Ala Ala Lys	
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ggg gtc aag ttg gag aat tat tac atc cag ccc atc tgc acg cct tcg	288
Gly Val Lys Leu Glu Asn Tyr Tyr Ile Gln Pro Ile Cys Thr Pro Ser	
85 90 95	
cgg agc cag ctc ctc act ggc agg tac cag atc cac aca gga ctc cag	336
Arg Ser Gln Leu Leu Thr Gly Arg Tyr Gln Ile His Thr Gly Leu Gln	
100 105 110	
cat tcc atc atc cgc cca cag cag ccc aac tgc ctg ccc ctg gac cag	384
His Ser Ile Ile Arg Pro Gln Gln Pro Asn Cys Leu Pro Leu Asp Gln	
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gtg aca ctg cca cag aag ctg cag gag gca ggt tat tcc acc cat atg	432
Val Thr Leu Pro Gln Lys Leu Gln Glu Ala Gly Tyr Ser Thr His Met	
130 135 140	
gtg ggc aag tgg cac ctg ggc ttc tac cgg aag gag tgt ctg ccc acc	480
Val Gly Lys Trp His Leu Gly Phe Tyr Arg Lys Glu Cys Leu Pro Thr	
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Arg Arg Gly Phe Asp Thr Phe Leu Gly Ser Leu Thr Gly Asn Val Asp	
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Tyr Tyr Thr Tyr Asp Asn Cys Asp Gly Pro Gly Val Cys Gly Phe Asp	
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Leu His Glu Gly Glu Asn Val Ala Trp Gly Leu Ser Gly Gln Tyr Ser	
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Thr Met Leu Tyr Ala Gln Arg Ala Ser His Ile Leu Ala Ser His Ser	
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Pro Gln Arg Pro Leu Phe Leu Tyr Val Ala Phe Gln Ala Val His Thr	
225 230 235 240	
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Pro Leu Gln Ser Pro Arg Glu Tyr Leu Tyr Arg Tyr Arg Thr Met Gly	
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Asn Val Ala Arg Arg Lys Tyr Ala Ala Met Val Thr Cys Met Asp Glu	
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Ala Val Arg Asn Ile Thr Trp Ala Leu Lys Arg Tyr Gly Phe Tyr Asn	
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Asn Ser Val Ile Ile Phe Ser Ser Asp Asn Gly Gly Gln Thr Phe Ser	
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ggg ggc agc aac tgg ccg ctc cga gga cgc aag ggc act tat tgg gaa	960
Gly Gly Ser Asn Trp Pro Leu Arg Gly Arg Lys Gly Thr Tyr Trp Glu	
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Gly Gly Val Arg Gly Leu Gly Phe Val His Ser Pro Leu Leu Lys Arg	
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Lys	Gln	Arg	Thr	Ser	Arg	Ala	Leu	Met	His	Ile	Thr	Asp	Trp	Tyr	Pro	
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Thr	Leu	Val	Gly	Leu	Ala	Gly	Gly	Thr	Thr	Ser	Ala	Ala	Asp	Gly	Leu	
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gat	ggc	tac	gac	gtg	tgg	ccg	gcc	atc	agc	gag	ggc	cgg	gcc	tca	cca	1152
Asp	Gly	Tyr	Asp	Val	Trp	Pro	Ala	Ile	Ser	Glu	Gly	Arg	Ala	Ser	Pro	
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Arg	Thr	Glu	Ile	Leu	His	Asn	Ile	Asp	Pro	Leu	Tyr	Asn	His	Ala	Gln	
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His	Gly	Ser	Leu	Glu	Gly	Gly	Phe	Gly	Ile	Trp	Asn	Thr	Ala	Val	Gln	
			405					410						415		
gct	gcc	atc	cgc	gtg	ggt	gag	tgg	aag	ctg	ctg	aca	gga	gac	ccc	ggc	1296
Ala	Ala	Ile	Arg	Val	Gly	Glu	Trp	Lys	Leu	Leu	Thr	Gly	Asp	Pro	Gly	
			420					425					430			
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Tyr	Gly	Asp	Trp	Ile	Pro	Pro	Gln	Thr	Leu	Ala	Thr	Phe	Pro	Gly	Ser	
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tgg	tgg	aac	ctg	gaa	cga	atg	gcc	agt	gtc	cgc	cag	gcc	gtg	tgg	ctc	1392
Trp	Trp	Asn	Leu	Glu	Arg	Met	Ala	Ser	Val	Arg	Gln	Ala	Val	Trp	Leu	
	450					455					460					
ttc	aac	atc	agt	gct	gac	cct	tat	gaa	cgg	gag	gac	ctg	gct	ggc	cag	1440
Phe	Asn	Ile	Ser	Ala	Asp	Pro	Tyr	Glu	Arg	Glu	Asp	Leu	Ala	Gly	Gln	
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cgg	cct	gat	gtg	gtc	cgc	acc	ctg	ctg	gct	cgc	ctg	gcc	gaa	tat	aac	1488
Arg	Pro	Asp	Val	Val	Arg	Thr	Leu	Leu	Ala	Arg	Leu	Ala	Glu	Tyr	Asn	
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cgc	aca	gcc	atc	ccg	gta	cgc	tac	cca	gct	gag	aac	ccc	cgg	gct	cat	1536
Arg	Thr	Ala	Ile	Pro	Val	Arg	Tyr	Pro	Ala	Glu	Asn	Pro	Arg	Ala	His	
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Pro	Asp	Phe	Asn	Gly	Gly	Ala	Trp	Gly	Pro	Trp	Ala	Ser	Asp	Glu	Glu	
		515					520					525				
gag	gag	gaa	gag	gaa	ggg	agg	gct	cga	agc	ttc	tcc	cgg	ggt	cgt	cgc	1632
Glu	Glu	Glu	Glu	Glu	Gly	Arg	Ala	Arg	Ser	Phe	Ser	Arg	Gly	Arg	Arg	
		530				535					540					
aag	aaa	aaa	tgc	aag	att	tgc	aag	ctt	cga	tcc	ttt	ttc	cgt	aaa	ctc	1680
Lys	Lys	Lys	Cys	Lys	Ile	Cys	Lys	Leu	Arg	Ser	Phe	Phe	Arg	Lys	Leu	
	545				550					555					560	
aac	acc	agg	cta	atg	tcc	caa	cgg	atc	tga							1710
Asn	Thr	Arg	Leu	Met	Ser	Gln	Arg	Ile	*							
				565												

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 <212> DNA
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<221> misc_feature
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 <223> n = A,T,C or G

<400> 16

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aggcacc atg gtg cag aag tcg cgc aac ggc ggc gta tac ccc ggc ccg 169
      Met Val Gln Lys Ser Arg Asn Gly Gly Val Tyr Pro Gly Pro
        1             5             10

agc ggg gag aag aag ctg aag gtg ggc ttc gtg ggg ctg gac ccc ggc 217
Ser Gly Glu Lys Lys Leu Lys Val Gly Phe Val Gly Leu Asp Pro Gly
  15             20             25             30

gcg ccc gac tcc acc cgg gac ggg gcg ctg ctg atc gcc ggc tcc gag 265
Ala Pro Asp Ser Thr Arg Asp Gly Ala Leu Leu Ile Ala Gly Ser Glu
             35             40             45

gcc ccc aag cgc ggc agc atc ctc agc aaa cct cgc gcg ggc ggc gcg 313
Ala Pro Lys Arg Gly Ser Ile Leu Ser Lys Pro Arg Ala Gly Gly Ala
             50             55             60

ggc gcc ggg aag ccc ccc aag cgc aac gcc ttc tac cgc aag ctg cag 361
Gly Ala Gly Lys Pro Pro Lys Arg Asn Ala Phe Tyr Arg Lys Leu Gln
        65             70             75

aat ttc ctc tac aac gtg ctg gag cgg ccg cgc ggc tgg gcg ttc atc 409
Asn Phe Leu Tyr Asn Val Leu Glu Arg Pro Arg Gly Trp Ala Phe Ile
      80             85             90

tac cac gcc tac gtg ttc ctc ctg gtt ttc tcc tgc ctc gtg ctg tct 457
Tyr His Ala Tyr Val Phe Leu Leu Val Phe Ser Cys Leu Val Leu Ser
      95             100             105             110

gtg ttt tcc acc atc aag gag tat gag aag agc tcg gag ggg gcc ctc 505
Val Phe Ser Thr Ile Lys Glu Tyr Glu Lys Ser Ser Glu Gly Ala Leu
             115             120             125

tac atc ctg gaa atc gtg act atc gtg gtg ttt ggc gtg gag tac ttc 553
Tyr Ile Leu Glu Ile Val Thr Ile Val Val Phe Gly Val Glu Tyr Phe
             130             135             140

gtg cgg atc tgg gcc gca ggc tgc tgc tgc cgg tac cgt ggc tgg agg 601
Val Arg Ile Trp Ala Ala Gly Cys Cys Cys Arg Tyr Arg Gly Trp Arg
             145             150             155

ggg cgg ctc aag ttt gcc cgg aaa ccg ttc tgt gtg att gac atc atg 649
Gly Arg Leu Lys Phe Ala Arg Lys Pro Phe Cys Val Ile Asp Ile Met
             160             165             170

gtg ctc atc gcc tcc att gcg gtg ctg gcc gcc ggc tcc cag ggc aac 697
Val Leu Ile Ala Ser Ile Ala Val Leu Ala Ala Gly Ser Gln Gly Asn
      175             180             185             190

gtc ttt gcc aca tct gcg ctc cgg agc ctg cgc ttc ctg cag att ctg 745
Val Phe Ala Thr Ser Ala Leu Arg Ser Leu Arg Phe Leu Gln Ile Leu
             195             200             205

cgg atg atc cgc atg gac cgg cgg gga ggc acc tgg aag ctg ctg ggc 793
Arg Met Ile Arg Met Asp Arg Arg Gly Gly Thr Trp Lys Leu Leu Gly
             210             215             220

tct gtg gtc tat gcc cac agc aag gag ctg gtc act gcc tgg tac atc 841
Ser Val Val Tyr Ala His Ser Lys Glu Leu Val Thr Ala Trp Tyr Ile
             225             230             235

ggc ttc ctt tgt ctc atc ctg gcc tcg ttc ctg gtg tac ttg gca gag 889
Gly Phe Leu Cys Leu Ile Leu Ala Ser Phe Leu Val Tyr Leu Ala Glu

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240	245	250	
aag ggg gag aac gac cac ttt gac acc tac gcg gat gca ctc tgg tgg			937
Lys Gly Glu Asn Asp His Phe Asp Thr Tyr Ala Asp Ala Leu Trp Trp			
255	260	265	270
ggc ctg atc acg ctg acc acc att ggc tac ggg gac aag tac ccc cag			985
Gly Leu Ile Thr Leu Thr Thr Ile Gly Tyr Gly Asp Lys Tyr Pro Gln			
	275	280	285
acc tgg aac ggc agg ctc ctt gcg gca acc ttc acc ctc atc ggt gtc			1033
Thr Trp Asn Gly Arg Leu Leu Ala Ala Thr Phe Thr Leu Ile Gly Val			
	290	295	300
tcc ttc ttc gcg ctg cct gca ggc atc ttg ggg tct ggg ttt gcc ctg			1081
Ser Phe Phe Ala Leu Pro Ala Gly Ile Leu Gly Ser Gly Phe Ala Leu			
	305	310	315
aag gtt cag gag cag cac agg cag aag cac ttt gag aag agg cgg aac			1129
Lys Val Gln Glu Gln His Arg Gln Lys His Phe Glu Lys Arg Arg Asn			
	320	325	330
ccg gca gca ggc ctg atc cag tcg gcc tgg aga ttc tac gcc acc aac			1177
Pro Ala Ala Gly Leu Ile Gln Ser Ala Trp Arg Phe Tyr Ala Thr Asn			
	335	340	350
ctc tcg cgc aca gac ctg cac tcc acg tgg cag tac tac gag cga acg			1225
Leu Ser Arg Thr Asp Leu His Ser Thr Trp Gln Tyr Tyr Glu Arg Thr			
	355	360	365
gtc acc gtg ccc atg tac agt tcg caa act caa acc tac ggg gcc tcc			1273
Val Thr Val Pro Met Tyr Ser Ser Gln Thr Gln Thr Tyr Gly Ala Ser			
	370	375	380
aga ctt atc ccc ccg ctg aac cag ctg gag ctg ctg agg aac ctc aag			1321
Arg Leu Ile Pro Pro Leu Asn Gln Leu Glu Leu Leu Arg Asn Leu Lys			
	385	390	395
agt aaa tct gga ctc gct ttc agg aag gac ccc ccg ccg gag ccg tct			1369
Ser Lys Ser Gly Leu Ala Phe Arg Lys Asp Pro Pro Pro Glu Pro Ser			
	400	405	410
cca agt aaa ggc agc ccg tgc aga ggg ccc ctg tgt gga tgc tgc ccc			1417
Pro Ser Lys Gly Ser Pro Cys Arg Gly Pro Cys Gly Cys Cys Pro			
	415	420	425
gga cgc tct agc cag aag gtc agt ttg aaa gat cgt gtc ttc tcc agc			1465
Gly Arg Ser Ser Gln Lys Val Ser Leu Lys Asp Arg Val Phe Ser Ser			
	435	440	445
ccc cga ggc gtg gct gcc aag ggg aag ggg tcc ccg cag gcc cag act			1513
Pro Arg Gly Val Ala Ala Lys Gly Lys Gly Ser Pro Gln Ala Gln Thr			
	450	455	460
gtg agg cgg tca ccc agc gcc gac cag agc ctc gag gac agc ccc agc			1561
Val Arg Arg Ser Pro Ser Ala Asp Gln Ser Leu Glu Asp Ser Pro Ser			
	465	470	475
aag gtg ccc aag agc tgg agc ttc ggg gac cgc agc cgg gca cgc cag			1609
Lys Val Pro Lys Ser Trp Ser Phe Gly Asp Arg Ser Arg Ala Arg Gln			
	480	485	490
gct ttc cgc atc aag ggt gcc gcg tca cgg cag aac tca gaa gaa gca			1657
Ala Phe Arg Ile Lys Gly Ala Ala Ser Arg Gln Asn Ser Glu Glu Ala			
	495	500	505
agc ctc ccc gga gag gac att gtg gat gac aag agc tgc ccc tgc gag			1705
Ser Leu Pro Gly Glu Asp Ile Val Asp Asp Lys Ser Cys Pro Cys Glu			
	515	520	525

ttt	gtg	acc	gag	gac	ctg	acc	ccg	ggc	ctc	aaa	gtc	agc	atc	aga	gcc	1753
Phe	Val	Thr	Glu	Asp	Leu	Thr	Pro	Gly	Leu	Lys	Val	Ser	Ile	Arg	Ala	
			530					535					540			
gtg	tgt	gtc	atg	cgg	ttc	ctg	gtg	tcc	aag	cgg	aag	ttc	aag	gag	agc	1801
Val	Cys	Val	Met	Arg	Phe	Leu	Val	Ser	Lys	Arg	Lys	Phe	Lys	Glu	Ser	
		545					550					555				
ctg	cgg	ccc	tac	gac	gtg	atg	gac	gtc	atc	gag	cag	tac	tca	gcc	ggc	1849
Leu	Arg	Pro	Tyr	Asp	Val	Met	Asp	Val	Ile	Glu	Gln	Tyr	Ser	Ala	Gly	
	560					565					570					
cac	ctg	gac	atg	ctg	tcc	cga	att	aag	agc	ctg	cag	tcc	aga	gtg	gac	1897
His	Leu	Asp	Met	Leu	Ser	Arg	Ile	Lys	Ser	Leu	Gln	Ser	Arg	Val	Asp	
575					580					585					590	
cag	atc	gtg	ggg	cgg	ggc	cca	gcg	atc	acg	gac	aag	gac	cgc	acc	aag	1945
Gln	Ile	Val	Gly	Arg	Gly	Pro	Ala	Ile	Thr	Asp	Lys	Asp	Arg	Thr	Lys	
				595					600					605		
ggc	ccg	gcc	gag	gcg	gag	ctg	ccc	gag	gac	ccc	agc	atg	atg	gga	cgg	1993
Gly	Pro	Ala	Glu	Ala	Glu	Leu	Pro	Glu	Asp	Pro	Ser	Met	Met	Gly	Arg	
			610					615					620			
ctc	ggg	aag	gtg	gag	aag	cag	gtc	ttg	tcc	atg	gag	aag	aag	ctg	gac	2041
Leu	Gly	Lys	Val	Glu	Lys	Gln	Val	Leu	Ser	Met	Glu	Lys	Lys	Leu	Asp	
		625					630						635			
ttc	ctg	gtg	aat	atc	tac	atg	cag	cgg	atg	ggc	atc	ccc	ccg	aca	gag	2089
Phe	Leu	Val	Asn	Ile	Tyr	Met	Gln	Arg	Met	Gly	Ile	Pro	Pro	Thr	Glu	
		640				645					650					
acc	gag	gcc	tac	ttt	ggg	gcc	aaa	gag	ccg	gag	ccg	gcg	ccg	ccg	tac	2137
Thr	Glu	Ala	Tyr	Phe	Gly	Ala	Lys	Glu	Pro	Glu	Pro	Ala	Pro	Pro	Tyr	
655					660					665					670	
cac	agc	ccg	gaa	gac	agc	cgg	gag	cat	gtc	gac	agg	cac	ggc	tgc	att	2185
His	Ser	Pro	Glu	Asp	Ser	Arg	Glu	His	Val	Asp	Arg	His	Gly	Cys	Ile	
				675					680					685		
gtc	aag	atc	gtg	cgc	tcc	agc	agc	tcc	acg	ggc	cag	aag	aac	ttc	tcg	2233
Val	Lys	Ile	Val	Arg	Ser	Ser	Ser	Ser	Thr	Gly	Gln	Lys	Asn	Phe	Ser	
			690					695					700			
gcg	ccc	ccg	gcc	gcg	ccc	cct	gtc	cag	tgt	ccg	ccc	tcc	acc	tcc	tgg	2281
Ala	Pro		Pro	Ala	Ala	Pro	Pro	Val	Gln	Cys	Pro	Pro	Ser	Thr	Trp	
		705					710						715			
cag	cca	cag	agc	cac	ccg	cgc	cag	ggc	cac	ggc	acc	tcc	ccc	gtg	ggg	2329
Gln	Pro	Gln	Ser	His	Pro	Arg	Gln	Gly	His	Gly	Thr	Ser	Pro	Val	Gly	
	720					725					730					
gac	cac	ggc	tcc	ctg	gtg	cgc	atc	ccg	ccg	ccg	cct	gcc	cac	gag	cgg	2377
Asp	His	Gly	Ser	Leu	Val	Arg	Ile	Pro	Pro	Pro	Pro	Ala	His	Glu	Arg	
735					740					745					750	
tcg	ctg	tcc	gcc	tac	ggc	ggg	ggc	aac	cgc	gcc	agc	atg	gag	ttc	ctg	2425
Ser	Leu	Ser	Ala	Tyr	Gly	Gly	Gly	Asn	Arg	Ala	Ser	Met	Glu	Phe	Leu	
				755					760					765		
cgg	cag	gag	gac	acc	ccg	ggc	tgc	agg	ccc	ccc	gag	ggg	aac	ctg	cgg	2473
Arg	Gln	Glu	Asp	Thr	Pro	Gly	Cys	Arg	Pro	Pro	Glu	Gly	Asn	Leu	Arg	
			770					775					780			
gac	agc	gac	acg	tcc	atc	tcc	atc	ccg	tcc	gtg	gac	cac	gag	gag	ctg	2521
Asp	Ser	Asp	Thr	Ser	Ile	Ser	Ile	Pro	Ser	Val	Asp	His	Glu	Glu	Leu	
		785					790						795			

gag cgt tcc ttc agc ggc ttc agc atc tcc cag tcc aag gag aac ctg 2569
 Glu Arg Ser Phe Ser Gly Phe Ser Ile Ser Gln Ser Lys Glu Asn Leu
 800 805 810

gat gct ctc aac agc tgc tac gcg gcc gtg gcg cct tgt gcc aaa gtc 2617
 Asp Ala Leu Asn Ser Cys Tyr Ala Ala Val Ala Pro Cys Ala Lys Val
 815 820 825 830

agg ccc tac att gcg gag gga gag tca gac acc gac tcc gac ctc tgt 2665
 Arg Pro Tyr Ile Ala Glu Gly Glu Ser Asp Thr Asp Ser Asp Leu Cys
 835 840 845

acc ccg tgc ggg ccc ccg cca cgc tgc gcc acc ggc gag ggt ccc ttt 2713
 Thr Pro Cys Gly Pro Pro Pro Arg Ser Ala Thr Gly Glu Gly Pro Phe
 850 855 860

ggt gac gtg ggc tgg gcc ggg ccc agg aag tga ggccggcgctg ggccagtggg 2766
 Gly Asp Val Gly Trp Ala Gly Pro Arg Lys *
 865 870

cccgcccgcg gccctcctca gcacgggtgcc tccgagggttt tgaggcgggga accctctggg 2826
 gcccttttct tacagtaact gagtgtggcg ggaagggtgg gccctggagg ggcccatgtg 2886
 ggctgaagga tggggggtcc tggcagtgac cttttacaaa agttattttc caacagggggc 2946
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 <212> PRT
 <213> Homo Sapiens

<400> 17
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 Asp Ser Thr Arg Asp Gly Ala Leu Leu Ile Ala Gly Ser Glu Ala Pro
 35 40 45
 Lys Arg Gly Ser Ile Leu Ser Lys Pro Arg Ala Gly Gly Ala Gly Ala
 50 55 60
 Gly Lys Pro Pro Lys Arg Asn Ala Phe Tyr Arg Lys Leu Gln Asn Phe
 65 70 75 80
 Leu Tyr Asn Val Leu Glu Arg Pro Arg Gly Trp Ala Phe Ile Tyr His
 85 90 95
 Ala Tyr Val Phe Leu Leu Val Phe Ser Cys Leu Val Leu Ser Val Phe
 100 105 110
 Ser Thr Ile Lys Glu Tyr Glu Lys Ser Ser Glu Gly Ala Leu Tyr Ile
 115 120 125
 Leu Glu Ile Val Thr Ile Val Val Phe Gly Val Glu Tyr Phe Val Arg
 130 135 140
 Ile Trp Ala Ala Gly Cys Cys Cys Arg Tyr Arg Gly Trp Arg Gly Arg
 145 150 155 160
 Leu Lys Phe Ala Arg Lys Pro Phe Cys Val Ile Asp Ile Met Val Leu
 165 170 175
 Ile Ala Ser Ile Ala Val Leu Ala Ala Gly Ser Gln Gly Asn Val Phe
 180 185 190
 Ala Thr Ser Ala Leu Arg Ser Leu Arg Phe Leu Gln Ile Leu Arg Met
 195 200 205
 Ile Arg Met Asp Arg Arg Gly Gly Thr Trp Lys Leu Leu Gly Ser Val
 210 215 220
 Val Tyr Ala His Ser Lys Glu Leu Val Thr Ala Trp Tyr Ile Gly Phe
 225 230 235 240
 Leu Cys Leu Ile Leu Ala Ser Phe Leu Val Tyr Leu Ala Glu Lys Gly
 245 250 255
 Glu Asn Asp His Phe Asp Thr Tyr Ala Asp Ala Leu Trp Trp Gly Leu
 260 265 270

Ile	Thr	Leu	Thr	Thr	Ile	Gly	Tyr	Gly	Asp	Lys	Tyr	Pro	Gln	Thr	Trp
		275					280					285			
Asn	Gly	Arg	Leu	Leu	Ala	Ala	Thr	Phe	Thr	Leu	Ile	Gly	Val	Ser	Phe
	290					295					300				
Phe	Ala	Leu	Pro	Ala	Gly	Ile	Leu	Gly	Ser	Gly	Phe	Ala	Leu	Lys	Val
305					310					315					320
Gln	Glu	Gln	His	Arg	Gln	Lys	His	Phe	Glu	Lys	Arg	Arg	Asn	Pro	Ala
				325					330					335	
Ala	Gly	Leu	Ile	Gln	Ser	Ala	Trp	Arg	Phe	Tyr	Ala	Thr	Asn	Leu	Ser
			340					345					350		
Arg	Thr	Asp	Leu	His	Ser	Thr	Trp	Gln	Tyr	Tyr	Glu	Arg	Thr	Val	Thr
		355					360					365			
Val	Pro	Met	Tyr	Ser	Ser	Gln	Thr	Gln	Thr	Tyr	Gly	Ala	Ser	Arg	Leu
	370					375					380				
Ile	Pro	Pro	Leu	Asn	Gln	Leu	Glu	Leu	Leu	Arg	Asn	Leu	Lys	Ser	Lys
385					390					395					400
Ser	Gly	Leu	Ala	Phe	Arg	Lys	Asp	Pro	Pro	Pro	Glu	Pro	Ser	Pro	Ser
				405				410						415	
Lys	Gly	Ser	Pro	Cys	Arg	Gly	Pro	Leu	Cys	Gly	Cys	Cys	Pro	Gly	Arg
			420					425					430		
Ser	Ser	Gln	Lys	Val	Ser	Leu	Lys	Asp	Arg	Val	Phe	Ser	Ser	Pro	Arg
		435					440					445			
Gly	Val	Ala	Ala	Lys	Gly	Lys	Gly	Ser	Pro	Gln	Ala	Gln	Thr	Val	Arg
	450					455					460				
Arg	Ser	Pro	Ser	Ala	Asp	Gln	Ser	Leu	Glu	Asp	Ser	Pro	Ser	Lys	Val
465					470					475					480
Pro	Lys	Ser	Trp	Ser	Phe	Gly	Asp	Arg	Ser	Arg	Ala	Arg	Gln	Ala	Phe
				485					490					495	
Arg	Ile	Lys	Gly	Ala	Ala	Ser	Arg	Gln	Asn	Ser	Glu	Glu	Ala	Ser	Leu
			500					505					510		
Pro	Gly	Glu	Asp	Ile	Val	Asp	Asp	Lys	Ser	Cys	Pro	Cys	Glu	Phe	Val
		515					520					525			
Thr	Glu	Asp	Leu	Thr	Pro	Gly	Leu	Lys	Val	Ser	Ile	Arg	Ala	Val	Cys
	530					535					540				
Val	Met	Arg	Phe	Leu	Val	Ser	Lys	Arg	Lys	Phe	Lys	Glu	Ser	Leu	Arg
545					550					555					560
Pro	Tyr	Asp	Val	Met	Asp	Val	Ile	Glu	Gln	Tyr	Ser	Ala	Gly	His	Leu
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Asp	Met	Leu	Ser	Arg	Ile	Lys	Ser	Leu	Gln	Ser	Arg	Val	Asp	Gln	Ile
			580					585					590		
Val	Gly	Arg	Gly	Pro	Ala	Ile	Thr	Asp	Lys	Asp	Arg	Thr	Lys	Gly	Pro
	595						600					605			
Ala	Glu	Ala	Glu	Leu	Pro	Glu	Asp	Pro	Ser	Met	Met	Gly	Arg	Leu	Gly
	610					615						620			
Lys	Val	Glu	Lys	Gln	Val	Leu	Ser	Met	Glu	Lys	Lys	Leu	Asp	Phe	Leu
625					630					635					640
Val	Asn	Ile	Tyr	Met	Gln	Arg	Met	Gly	Ile	Pro	Pro	Thr	Glu	Thr	Glu
				645					650					655	
Ala	Tyr	Phe	Gly	Ala	Lys	Glu	Pro	Glu	Pro	Ala	Pro	Pro	Tyr	His	Ser
			660					665					670		
Pro	Glu	Asp	Ser	Arg	Glu	His	Val	Asp	Arg	His	Gly	Cys	Ile	Val	Lys
		675					680					685			
Ile	Val	Arg	Ser	Ser	Ser	Ser	Thr	Gly	Gln	Lys	Asn	Phe	Ser	Ala	Pro
	690					695						700			
Pro	Ala	Ala	Pro	Pro	Val	Gln	Cys	Pro	Pro	Ser	Thr	Ser	Trp	Gln	Pro
705					710						715				720
Gln	Ser	His	Pro	Arg	Gln	Gly	His	Gly	Thr	Ser	Pro	Val	Gly	Asp	His
				725					730					735	
Gly	Ser	Leu	Val	Arg	Ile	Pro	Pro	Pro	Pro	Ala	His	Glu	Arg	Ser	Leu
			740					745					750		
Ser	Ala	Tyr	Gly	Gly	Gly	Asn	Arg	Ala	Ser	Met	Glu	Phe	Leu	Arg	Gln
	755						760					765			
Glu	Asp	Thr	Pro	Gly	Cys	Arg	Pro	Pro	Glu	Gly	Asn	Leu	Arg	Asp	Ser
	770					775					780				
Asp	Thr	Ser	Ile	Ser	Ile	Pro	Ser	Val	Asp	His	Glu	Glu	Leu	Glu	Arg
785					790					795					800
Ser	Phe	Ser	Gly	Phe	Ser	Ile	Ser	Gln	Ser	Lys	Glu	Asn	Leu	Asp	Ala
				805					810					815	
Leu	Asn	Ser	Cys	Tyr	Ala	Ala	Val	Ala	Pro	Cys	Ala	Lys	Val	Arg	Pro

Tyr Ile Ala Glu Gly Glu Ser Asp Thr Asp Ser Asp Leu Cys Thr Pro
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 Cys Gly Pro Pro Pro Arg Ser Ala Thr Gly Glu Gly Pro Phe Gly Asp
 850 855 860
 Val Gly Trp Ala Gly Pro Arg Lys
 865 870

<210> 18
 <211> 2619
 <212> DNA
 <213> Homo Sapiens

<220>
 <221> CDS
 <222> (1)...(2619)

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 gag aag aag ctg aag gtg ggc ttc gtg ggg ctg gac ccc ggc gcg ccc 96
 Glu Lys Lys Leu Lys Val Gly Phe Val Gly Leu Asp Pro Gly Ala Pro
 20 25 30
 gac tcc acc cgg gac ggg gcg ctg ctg atc gcc ggc tcc gag gcc ccc 144
 Asp Ser Thr Arg Asp Gly Ala Leu Leu Ile Ala Gly Ser Glu Ala Pro
 35 40 45
 aag cgc ggc agc atc ctc agc aaa cct cgc gcg ggc ggc gcg ggc gcc 192
 Lys Arg Gly Ser Ile Leu Ser Lys Pro Arg Ala Gly Gly Ala Gly Ala
 50 55 60
 ggg aag ccc ccc aag cgc aac gcc ttc tac cgc aag ctg cag aat ttc 240
 Gly Lys Pro Pro Lys Arg Asn Ala Phe Tyr Arg Lys Leu Gln Asn Phe
 65 70 75 80
 ctc tac aac gtg ctg gag cgg ccg cgc ggc tgg gcg ttc atc tac cac 288
 Leu Tyr Asn Val Leu Glu Arg Pro Arg Gly Trp Ala Phe Ile Tyr His
 85 90 95
 gcc tac gtg ttc ctc ctg gtt ttc tcc tgc ctc gtg ctg tct gtg ttt 336
 Ala Tyr Val Phe Leu Leu Val Phe Ser Cys Leu Val Leu Ser Val Phe
 100 105 110
 tcc acc atc aag gag tat gag aag agc tcg gag ggg gcc ctc tac atc 384
 Ser Thr Ile Lys Glu Tyr Glu Lys Ser Ser Glu Gly Ala Leu Tyr Ile
 115 120 125
 ctg gaa atc gtg act atc gtg gtg ttt ggc gtg gag tac ttc gtg cgg 432
 Leu Glu Ile Val Thr Ile Val Val Phe Gly Val Glu Tyr Phe Val Arg
 130 135 140
 atc tgg gcc gca ggc tgc tgc tgc cgg tac cgt gcc tgg agg ggg cgg 480
 Ile Trp Ala Ala Gly Cys Cys Cys Arg Tyr Arg Gly Trp Arg Gly Arg
 145 150 155 160
 ctc aag ttt gcc cgg aaa ccg ttc tgt gtg att gac atc atg gtg ctc 528
 Leu Lys Phe Ala Arg Lys Pro Phe Cys Val Ile Asp Ile Met Val Leu
 165 170 175
 atc gcc tcc att gcg gtg ctg gcc gcc ggc tcc cag gcc aac gtc ttt 576
 Ile Ala Ser Ile Ala Val Leu Ala Ala Gly Ser Gln Gly Asn Val Phe
 180 185 190
 gcc aca tct gcg ctc cgg agc ctg cgc ttc ctg cag att ctg cgg atg 624
 Ala Thr Ser Ala Leu Arg Ser Leu Arg Phe Leu Gln Ile Leu Arg Met

195					200					205						
atc	cgc	atg	gac	cgg	cgg	gga	ggc	acc	tgg	aag	ctg	ctg	ggc	tct	gtg	672
Ile	Arg	Met	Asp	Arg	Arg	Gly	Gly	Thr	Trp	Lys	Leu	Leu	Gly	Ser	Val	
	210					215					220					
gtc	tat	gcc	cac	agc	aag	gag	ctg	gtc	act	gcc	tgg	tac	atc	ggc	ttc	720
Val	Tyr	Ala	His	Ser	Lys	Glu	Leu	Val	Thr	Ala	Trp	Tyr	Ile	Gly	Phe	
	225				230					235					240	
ctt	tgt	ctc	atc	ctg	gcc	tcg	ttc	ctg	gtg	tac	ttg	gca	gag	aag	ggg	768
Leu	Cys	Leu	Ile	Leu	Ala	Ser	Phe	Leu	Val	Tyr	Leu	Ala	Glu	Lys	Gly	
				245					250					255		
gag	aac	gac	cac	ttt	gac	acc	tac	gcg	gat	gca	ctc	tgg	tgg	ggc	ctg	816
Glu	Asn	Asp	His	Phe	Asp	Thr	Tyr	Ala	Asp	Ala	Leu	Trp	Trp	Gly	Leu	
			260					265					270			
atc	acg	ctg	acc	acc	att	ggc	tac	ggg	gac	aag	tac	ccc	cag	acc	tgg	864
Ile	Thr	Leu	Thr	Thr	Ile	Gly	Tyr	Gly	Asp	Lys	Tyr	Pro	Gln	Thr	Trp	
		275					280					285				
aac	ggc	agg	ctc	ctt	gcg	gca	acc	ttc	acc	ctc	atc	ggt	gtc	tcc	ttc	912
Asn	Gly	Arg	Leu	Leu	Ala	Ala	Thr	Phe	Thr	Leu	Ile	Gly	Val	Ser	Phe	
	290					295					300					
ttc	gcg	ctg	cct	gca	ggc	atc	ttg	ggg	tct	ggg	ttt	gcc	ctg	aag	gtt	960
Phe	Ala	Leu	Pro	Ala	Gly	Ile	Leu	Gly	Ser	Gly	Phe	Ala	Leu	Lys	Val	
	305				310					315					320	
cag	gag	cag	cac	agg	cag	aag	cac	ttt	gag	aag	agg	cgg	aac	ccg	gca	1008
Gln	Glu	Gln	His	Arg	Gln	Lys	His	Phe	Glu	Lys	Arg	Arg	Asn	Pro	Ala	
				325					330					335		
gca	ggc	ctg	atc	cag	tcg	gcc	tgg	aga	ttc	tac	gcc	acc	aac	ctc	tcg	1056
Ala	Gly	Leu	Ile	Gln	Ser	Ala	Trp	Arg	Phe	Tyr	Ala	Thr	Asn	Leu	Ser	
				340				345					350			
cgc	aca	gac	ctg	cac	tcc	acg	tgg	cag	tac	tac	gag	cga	acg	gtc	acc	1104
Arg	Thr	Asp	Leu	His	Ser	Thr	Trp	Gln	Tyr	Tyr	Glu	Arg	Thr	Val	Thr	
		355					360					365				
gtg	ccc	atg	tac	agt	tcg	caa	act	caa	acc	tac	ggg	gcc	tcc	aga	ctt	1152
Val	Pro	Met	Tyr	Ser	Ser	Gln	Thr	Gln	Thr	Tyr	Gly	Ala	Ser	Arg	Leu	
	370					375					380					
atc	ccc	ccg	ctg	aac	cag	ctg	gag	ctg	ctg	agg	aac	ctc	aag	agt	aaa	1200
Ile	Pro	Pro	Leu	Asn	Gln	Leu	Glu	Leu	Leu	Arg	Asn	Leu	Lys	Ser	Lys	
	385				390					395					400	
tct	gga	ctc	gct	ttc	agg	aag	gac	ccc	ccg	ccg	gag	ccg	tct	cca	agt	1248
Ser	Gly	Leu	Ala	Phe	Arg	Lys	Asp	Pro	Pro	Pro	Glu	Pro	Ser	Pro	Ser	
				405					410					415		
aaa	ggc	agc	ccg	tgc	aga	ggg	ccc	ctg	tgt	gga	tgc	tgc	ccc	gga	cgc	1296
Lys	Gly	Ser	Pro	Cys	Arg	Gly	Pro	Leu	Cys	Gly	Cys	Cys	Pro	Gly	Arg	
			420					425					430			
tct	agc	cag	aag	gtc	agt	ttg	aaa	gat	cgt	gtc	ttc	tcc	agc	ccc	cga	1344
Ser	Ser	Gln	Lys	Val	Ser	Leu	Lys	Asp	Arg	Val	Phe	Ser	Ser	Pro	Arg	
		435					440					445				
ggc	gtg	gct	gcc	aag	ggg	aag	ggg	tcc	ccg	cag	gcc	cag	act	gtg	agg	1392
Gly	Val	Ala	Ala	Lys	Gly	Lys	Gly	Ser	Pro	Gln	Ala	Gln	Thr	Val	Arg	
	450					455					460					
cgg	tca	ccc	agc	gcc	gac	cag	agc	ctc	gag	gac	agc	ccc	agc	aag	gtg	1440
Arg	Ser	Pro	Ser	Ala	Asp	Gln	Ser	Leu	Glu	Asp	Ser	Pro	Ser	Lys	Val	
	465				470					475					480	

ccc aag agc tgg agc ttc ggg gac cgc agc cgg gca cgc cag gct ttc	1488
Pro Lys Ser Trp Ser Phe Gly Asp Arg Ser Arg Ala Arg Gln Ala Phe	
485 490 495	
cgc atc aag ggt gcc gcg tca cgg cag aac tca gaa gaa gca agc ctc	1536
Arg Ile Lys Gly Ala Ala Ser Arg Gln Asn Ser Glu Glu Ala Ser Leu	
500 505 510	
ccc gga gag gac att gtg gat gac aag agc tgc ccc tgc gag ttt gtg	1584
Pro Gly Glu Asp Ile Val Asp Asp Lys Ser Cys Pro Cys Glu Phe Val	
515 520 525	
acc gag gac ctg acc ccg ggc ctc aaa gtc agc atc aga gcc gtg tgt	1632
Thr Glu Asp Leu Thr Pro Gly Leu Lys Val Ser Ile Arg Ala Val Cys	
530 535 540	
gtc atg cgg ttc ctg gtg tcc aag cgg aag ttc aag gag agc ctg cgg	1680
Val Met Arg Phe Leu Val Ser Lys Arg Lys Phe Lys Glu Ser Leu Arg	
545 550 555 560	
ccc tac gac gtg atg gac gtc atc gag cag tac tca gcc ggc cac ctg	1728
Pro Tyr Asp Val Met Asp Val Ile Glu Gln Tyr Ser Ala Gly His Leu	
565 570 575	
gac atg ctg tcc cga att aag agc ctg cag tcc aga gtg gac cag atc	1776
Asp Met Leu Ser Arg Ile Lys Ser Leu Gln Ser Arg Val Asp Gln Ile	
580 585 590	
gtg ggg cgg ggc cca gcg atc acg gac aag gac cgc acc aag ggc ccg	1824
Val Gly Arg Gly Pro Ala Ile Thr Asp Lys Asp Arg Thr Lys Gly Pro	
595 600 605	
gcc gag gcg gag ctg ccc gag gac ccc agc atg atg gga cgg ctc ggg	1872
Ala Glu Ala Glu Leu Pro Glu Asp Pro Ser Met Met Gly Arg Leu Gly	
610 615 620	
aag gtg gag aag cag gtc ttg tcc atg gag aag aag ctg gac ttc ctg	1920
Lys Val Glu Lys Gln Val Leu Ser Met Glu Lys Lys Leu Asp Phe Leu	
625 630 635 640	
gtg aat atc tac atg cag cgg atg ggc atc ccc ccg aca gag acc gag	1968
Val Asn Ile Tyr Met Gln Arg Met Gly Ile Pro Pro Thr Glu Thr Glu	
645 650 655	
gcc tac ttt ggg gcc aaa gag ccg gag ccg gcg ccg ccg tac cac agc	2016
Ala Tyr Phe Gly Ala Lys Glu Pro Glu Pro Ala Pro Pro Tyr His Ser	
660 665 670	
ccg gaa gac agc cgg gag cat gtc gac agg cac ggc tgc att gtc aag	2064
Pro Glu Asp Ser Arg Glu His Val Asp Arg His Gly Cys Ile Val Lys	
675 680 685	
atc gtg cgc tcc agc agc tcc acg ggc cag aag aac ttc tcg gcg ccc	2112
Ile Val Arg Ser Ser Ser Ser Thr Gly Gln Lys Asn Phe Ser Ala Pro	
690 695 700	
ccg gcc gcg ccc cct gtc cag tgt ccg ccc tcc acc tcc tgg cag cca	2160
Pro Ala Ala Pro Pro Val Gln Cys Pro Pro Ser Thr Ser Trp Gln Pro	
705 710 715 720	
cag agc cac ccg cgc cag ggc cac ggc acc tcc ccc gtg ggg gac cac	2208
Gln Ser His Pro Arg Gln Gly His Gly Thr Ser Pro Val Gly Asp His	
725 730 735	
ggc tcc ctg gtg cgc atc ccg ccg ccg cct gcc cac gag cgg tcg ctg	2256
Gly Ser Leu Val Arg Ile Pro Pro Pro Pro Ala His Glu Arg Ser Leu	
740 745 750	

tcc gcc tac ggc ggg ggc aac cgc gcc agc atg gag ttc ctg cgg cag 2304
 Ser Ala Tyr Gly Gly Gly Asn Arg Ala Ser Met Glu Phe Leu Arg Gln
 755 760 765

gag gac acc ccg ggc tgc agg ccc ccc gag ggg aac ctg cgg gac agc 2352
 Glu Asp Thr Pro Gly Cys Arg Pro Pro Glu Gly Asn Leu Arg Asp Ser
 770 775 780

gac acg tcc atc tcc atc ccg tcc gtg gac cac gag gag ctg gag cgt 2400
 Asp Thr Ser Ile Ser Ile Pro Ser Val Asp His Glu Glu Leu Glu Arg
 785 790 795 800

tcc ttc agc ggc ttc agc atc tcc cag tcc aag gag aac ctg gat gct 2448
 Ser Phe Ser Gly Phe Ser Ile Ser Gln Ser Lys Glu Asn Leu Asp Ala
 805 810 815

ctc aac agc tgc tac gcg gcc gtg gcg cct tgt gcc aaa gtc agg ccc 2496
 Leu Asn Ser Cys Tyr Ala Ala Val Ala Pro Cys Ala Lys Val Arg Pro
 820 825 830

tac att gcg gag gga gag tca gac acc gac tcc gac ctc tgt acc ccg 2544
 Tyr Ile Ala Glu Gly Glu Ser Asp Thr Asp Ser Asp Leu Cys Thr Pro
 835 840 845

tgc ggg ccc ccg cca cgc tcg gcc acc ggc gag ggt ccc ttt ggt gac 2592
 Cys Gly Pro Pro Pro Arg Ser Ala Thr Gly Glu Gly Pro Phe Gly Asp
 850 855 860

gtg ggc tgg gcc ggg ccc agg aag tga 2619
 Val Gly Trp Ala Gly Pro Arg Lys *
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ggc cct acc tgc gcc ccg agc gcc tgc ctg ccc ccc aac agc agc gcc 97
 Gly Pro Thr Cys Ala Pro Ser Ala Cys Leu Pro Pro Asn Ser Ser Ala
 15 20 25

tgg ttt ccc ggc tgg gcc gag ccc gac agc aac ggc agc gcc gcc tcg 145
 Trp Phe Pro Gly Trp Ala Glu Pro Asp Ser Asn Gly Ser Ala Gly Ser
 30 35 40

gag gac gcg cag ctg gag ccc gcg cac atc tcc ccg gcc atc ccg gtc 193
 Glu Asp Ala Gln Leu Glu Pro Ala His Ile Ser Pro Ala Ile Pro Val
 45 50 55 60

atc atc acg gcg gtc tac tcc gta gtg ttc gtc gtg ggc ttg gtg ggc 241
 Ile Ile Thr Ala Val Tyr Ser Val Val Phe Val Val Gly Leu Val Gly
 65 70 75

aac tcg ctg gtc atg ttc gtg atc atc cga tac aca aag atg aag aca 289
 Asn Ser Leu Val Met Phe Val Ile Ile Arg Tyr Thr Lys Met Lys Thr
 80 85 90

gca acc aac att tac ata ttt aac ctg gct ttg gca gat gct tta gtt 337
 Ala Thr Asn Ile Tyr Ile Phe Asn Leu Ala Leu Ala Asp Ala Leu Val

	95		100		105											
act	aca	acc	atg	ccc	ttt	cag	agt	acg	gtc	tac	ttg	atg	aat	tcc	tgg	385
Thr	Thr	Thr	Met	Pro	Phe	Gln	Ser	Thr	Val	Tyr	Leu	Met	Asn	Ser	Trp	
	110					115					120					
cct	ttt	ggg	gat	gtg	ctg	tgc	aag	ata	gta	att	tcc	att	gat	tac	tac	433
Pro	Phe	Gly	Asp	Val	Leu	Cys	Lys	Ile	Val	Ile	Ser	Ile	Asp	Tyr	Tyr	
	125				130					135					140	
aac	atg	ttc	acc	agc	atc	ttc	acc	ttg	acc	atg	atg	agc	gtg	gac	cgc	481
Asn	Met	Phe	Thr	Ser	Ile	Phe	Thr	Leu	Thr	Met	Met	Ser	Val	Asp	Arg	
				145					150					155		
tac	att	gcc	gtg	tgc	cac	ccc	gtg	aag	gct	ttg	gac	ttc	cgc	aca	ccc	529
Tyr	Ile	Ala	Val	Cys	His	Pro	Val	Lys	Ala	Leu	Asp	Phe	Arg	Thr	Pro	
			160					165					170			
ttg	aag	gca	aag	atc	atc	aat	atc	tgc	atc	tggt	ctg	ctg	tcg	tca	tct	577
Leu	Lys	Ala	Lys	Ile	Ile	Asn	Ile	Cys	Ile	Trp	Leu	Leu	Ser	Ser	Ser	
		175					180					185				
gtt	ggc	atc	tct	gca	ata	gtc	ctt	gga	ggc	acc	aaa	gtc	agg	gaa	gac	625
Val	Gly	Ile	Ser	Ala	Ile	Val	Leu	Gly	Gly	Thr	Lys	Val	Arg	Glu	Asp	
	190					195					200					
gtc	gat	gtc	att	gag	tgc	tcc	ttg	cag	ttc	cca	gat	gat	gac	tac	tcc	673
Val	Asp	Val	Ile	Glu	Cys	Ser	Leu	Gln	Phe	Pro	Asp	Asp	Asp	Tyr	Ser	
	205				210					215					220	
tggt	tggt	gac	ctc	ttc	atg	aag	atc	tgc	gtc	ttc	atc	ttt	gcc	ttc	gtg	721
Trp	Trp	Asp	Leu	Phe	Met	Lys	Ile	Cys	Val	Phe	Ile	Phe	Ala	Phe	Val	
			225						230					235		
atc	cct	gtc	ctc	atc	atc	atc	gtc	tgc	tac	acc	ctg	atg	atc	ctg	cgt	769
Ile	Pro	Val	Leu	Ile	Ile	Ile	Val	Cys	Tyr	Thr	Leu	Met	Ile	Leu	Arg	
			240					245					250			
ctc	aag	agc	gtc	cgg	ctc	ctt	tct	ggc	tcc	cga	gag	aaa	gat	cgc	aac	817
Leu	Lys	Ser	Val	Arg	Leu	Leu	Ser	Gly	Ser	Arg	Glu	Lys	Asp	Arg	Asn	
		255					260					265				
ctg	cgt	agg	atc	acc	aga	ctg	gtc	ctg	gtg	gtg	gtg	gcg	gtt	ttc	gtc	865
Leu	Arg	Arg	Ile	Thr	Arg	Leu	Val	Leu	Val	Val	Val	Ala	Val	Phe	Val	
	270					275					280					
gtc	tgc	tggt	act	ccc	att	cac	ata	ttc	atc	ctg	gtg	gag	gct	ctg	ggg	913
Val	Cys	Trp	Thr	Pro	Ile	His	Ile	Phe	Ile	Leu	Val	Glu	Ala	Leu	Gly	
	285				290					295					300	
agc	acc	tcc	cac	agc	aca	gct	gct	ctc	tcc	agc	tat	tac	ttc	tgc	atc	961
Ser	Thr	Ser	His	Ser	Thr	Ala	Ala	Leu	Ser	Ser	Tyr	Tyr	Phe	Cys	Ile	
				305					310					315		
gcc	tta	ggc	tat	acc	aac	agt	agc	ctg	aat	ccc	att	ctc	tac	gcc	ttt	1009
Ala	Leu	Gly	Tyr	Thr	Asn	Ser	Ser	Leu	Asn	Pro	Ile	Leu	Tyr	Ala	Phe	
			320					325					330			
ctt	gat	gaa	aac	ttc	aag	cgg	tgt	ttc	cgg	gac	ttc	tgc	ttt	cca	ctg	1057
Leu	Asp	Glu	Asn	Phe	Lys	Arg	Cys	Phe	Arg	Asp	Phe	Cys	Phe	Pro	Leu	
		335					340					345				
aag	atg	agg	atg	gag	cgg	cag	agc	act	agc	aga	gtc	cga	aat	aca	gtt	1105
Lys	Met	Arg	Met	Glu	Arg	Gln	Ser	Thr	Ser	Arg	Val	Arg	Asn	Thr	Val	
	350					355					360					
cag	gat	cct	gct	tac	ctg	agg	gac	atc	gat	ggg	atg	aat	aaa	cca	gta	1153
Gln	Asp	Pro	Ala	Tyr	Leu	Arg	Asp	Ile	Asp	Gly	Met	Asn	Lys	Pro	Val	
	365				370					375					380	

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1182

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 <212> PRT
 <213> Homo Sapiens

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 Trp Ala Glu Pro Asp Ser Asn Gly Ser Ala Gly Ser Glu Asp Ala Gln
 35 40 45
 Leu Glu Pro Ala His Ile Ser Pro Ala Ile Pro Val Ile Ile Thr Ala
 50 55 60
 Val Tyr Ser Val Val Phe Val Val Gly Leu Val Gly Asn Ser Leu Val
 65 70 75
 Met Phe Val Ile Ile Arg Tyr Thr Lys Met Lys Thr Ala Thr Asn Ile
 85 90 95
 Tyr Ile Phe Asn Leu Ala Leu Ala Asp Ala Leu Val Thr Thr Thr Met
 100 105 110
 Pro Phe Gln Ser Thr Val Tyr Leu Met Asn Ser Trp Pro Phe Gly Asp
 115 120 125
 Val Leu Cys Lys Ile Val Ile Ser Ile Asp Tyr Tyr Asn Met Phe Thr
 130 135 140
 Ser Ile Phe Thr Leu Thr Met Met Ser Val Asp Arg Tyr Ile Ala Val
 145 150 155
 Cys His Pro Val Lys Ala Leu Asp Phe Arg Thr Pro Leu Lys Ala Lys
 165 170 175
 Ile Ile Asn Ile Cys Ile Trp Leu Leu Ser Ser Ser Val Gly Ile Ser
 180 185 190
 Ala Ile Val Leu Gly Gly Thr Lys Val Arg Glu Asp Val Asp Val Ile
 195 200 205
 Glu Cys Ser Leu Gln Phe Pro Asp Asp Asp Tyr Ser Trp Trp Asp Leu
 210 215 220
 Phe Met Lys Ile Cys Val Phe Ile Phe Ala Phe Val Ile Pro Val Leu
 225 230 235
 Ile Ile Ile Val Cys Tyr Thr Leu Met Ile Leu Arg Leu Lys Ser Val
 245 250 255
 Arg Leu Leu Ser Gly Ser Arg Glu Lys Asp Arg Asn Leu Arg Arg Ile
 260 265 270
 Thr Arg Leu Val Leu Val Val Ala Val Phe Val Val Cys Trp Thr
 275 280 285
 Pro Ile His Ile Phe Ile Leu Val Glu Ala Leu Gly Ser Thr Ser His
 290 295 300
 Ser Thr Ala Ala Leu Ser Ser Tyr Tyr Phe Cys Ile Ala Leu Gly Tyr
 305 310 315
 Thr Asn Ser Ser Leu Asn Pro Ile Leu Tyr Ala Phe Leu Asp Glu Asn
 325 330 335
 Phe Lys Arg Cys Phe Arg Asp Phe Cys Phe Pro Leu Lys Met Arg Met
 340 345 350
 Glu Arg Gln Ser Thr Ser Arg Val Arg Asn Thr Val Gln Asp Pro Ala
 355 360 365
 Tyr Leu Arg Asp Ile Asp Gly Met Asn Lys Pro Val
 370 375 380

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gcc ccg agc gcc tgc ctg ccc ccc aac agc agc gcc tgg ttt ccc ggc	96
Ala Pro Ser Ala Cys Leu Pro Pro Asn Ser Ser Ala Trp Phe Pro Gly	
20 25 30	
tgg gcc gag ccc gac agc aac ggc agc gcc ggc tcg gag gac gcg cag	144
Trp Ala Glu Pro Asp Ser Asn Gly Ser Ala Gly Ser Glu Asp Ala Gln	
35 40 45	
ctg gag ccc gcg cac atc tcc ccg gcc atc ccg gtc atc atc acg gcg	192
Leu Glu Pro Ala His Ile Ser Pro Ala Ile Pro Val Ile Ile Thr Ala	
50 55 60	
gtc tac tcc gta gtg ttc gtc gtg ggc ttg gtg ggc aac tcg ctg gtc	240
Val Tyr Ser Val Val Phe Val Val Gly Leu Val Gly Asn Ser Leu Val	
65 70 75 80	
atg ttc gtg atc atc cga tac aca aag atg aag aca gca acc aac att	288
Met Phe Val Ile Ile Arg Tyr Thr Lys Met Lys Thr Ala Thr Asn Ile	
85 90 95	
tac ata ttt aac ctg gct ttg gca gat gct tta gtt act aca acc atg	336
Tyr Ile Phe Asn Leu Ala Leu Ala Asp Ala Leu Val Thr Thr Thr Met	
100 105 110	
ccc ttt cag agt acg gtc tac ttg atg aat tcc tgg cct ttt ggg gat	384
Pro Phe Gln Ser Thr Val Tyr Leu Met Asn Ser Trp Pro Phe Gly Asp	
115 120 125	
gtg ctg tgc aag ata gta att tcc att gat tac tac aac atg ttc acc	432
Val Leu Cys Lys Ile Val Ile Ser Ile Asp Tyr Tyr Asn Met Phe Thr	
130 135 140	
agc atc ttc acc ttg acc atg atg agc gtg gac cgc tac att gcc gtg	480
Ser Ile Phe Thr Leu Thr Met Met Ser Val Asp Arg Tyr Ile Ala Val	
145 150 155 160	
tgc cac ccc gtg aag gct ttg gac ttc cgc aca ccc ttg aag gca aag	528
Cys His Pro Val Lys Ala Leu Asp Phe Arg Thr Pro Leu Lys Ala Lys	
165 170 175	
atc atc aat atc tgc atc tgg ctg ctg tcg tca tct gtt ggc atc tct	576
Ile Ile Asn Ile Cys Ile Trp Leu Leu Ser Ser Ser Val Gly Ile Ser	
180 185 190	
gca ata gtc ctt gga ggc acc aaa gtc agg gaa gac gtc gat gtc att	624
Ala Ile Val Leu Gly Gly Thr Lys Val Arg Glu Asp Val Asp Val Ile	
195 200 205	
gag tgc tcc ttg cag ttc cca gat gat gac tac tcc tgg tgg gac ctc	672
Glu Cys Ser Leu Gln Phe Pro Asp Asp Asp Tyr Ser Trp Trp Asp Leu	
210 215 220	
ttc atg aag atc tgc gtc ttc atc ttt gcc ttc gtg atc cct gtc ctc	720
Phe Met Lys Ile Cys Val Phe Ile Phe Ala Phe Val Ile Pro Val Leu	
225 230 235 240	
atc atc atc gtc tgc tac acc ctg atg atc ctg cgt ctc aag agc gtc	768
Ile Ile Ile Val Cys Tyr Thr Leu Met Ile Leu Arg Leu Lys Ser Val	
245 250 255	
cgg ctc ctt tct ggc tcc cga gag aaa gat cgc aac ctg cgt agg atc	816
Arg Leu Leu Ser Gly Ser Arg Glu Lys Asp Arg Asn Leu Arg Arg Ile	

260	265	270	
acc aga ctg gtc ctg gtg gtg gtg gcg gtt ttc gtc gtc tgc tgg act			864
Thr Arg Leu Val Leu Val Val Val Ala Val Phe Val Val Cys Trp Thr			
275	280	285	
ccc att cac ata ttc atc ctg gtg gag gct ctg ggg agc acc tcc cac			912
Pro Ile His Ile Phe Ile Leu Val Glu Ala Leu Gly Ser Thr Ser His			
290	295	300	
agc aca gct gct ctc tcc agc tat tac ttc tgc atc gcc tta ggc tat			960
Ser Thr Ala Ala Leu Ser Ser Tyr Tyr Phe Cys Ile Ala Leu Gly Tyr			
305	310	315	320
acc aac agt agc ctg aat ccc att ctc tac gcc ttt ctt gat gaa aac			1008
Thr Asn Ser Ser Leu Asn Pro Ile Leu Tyr Ala Phe Leu Asp Glu Asn			
	325	330	335
ttc aag cgg tgt ttc cgg gac ttc tgc ttt cca ctg aag atg agg atg			1056
Phe Lys Arg Cys Phe Arg Asp Phe Cys Phe Pro Leu Lys Met Arg Met			
	340	345	350
gag cgg cag agc act agc aga gtc cga aat aca gtt cag gat cct gct			1104
Glu Arg Gln Ser Thr Ser Arg Val Arg Asn Thr Val Gln Asp Pro Ala			
	355	360	365
tac ctg agg gac atc gat ggg atg aat aaa cca gta tga			1143
Tyr Leu Arg Asp Ile Asp Gly Met Asn Lys Pro Val *			
370	375	380	
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	Met Ala Asp Gly Ala Lys Ala		
	1	5	
aac ccc aaa ggg ttc aaa aag aag gtg ctg gat aga tgc ttc tct ggg			161
Asn Pro Lys Gly Phe Lys Lys Lys Val Leu Asp Arg Cys Phe Ser Gly			
	10	15	20
tgg agg ggc cca cgc ttc ggg gcc tcc tgt cct tca aga acc tcc agg			209
Trp Arg Gly Pro Arg Phe Gly Ala Ser Cys Pro Ser Arg Thr Ser Arg			
	25	30	35
tct agc ctg ggt atg aag aag ttc ttc acc gtg gcc atc ctt gct ggc			257
Ser Ser Leu Gly Met Lys Lys Phe Phe Thr Val Ala Ile Leu Ala Gly			
	40	45	50
agc gtt ctg tcc aca gct cac ggc agc ctg ctc aac ctg aag gcc atg			305
Ser Val Leu Ser Thr Ala His Gly Ser Leu Leu Asn Leu Lys Ala Met			
	60	65	70
gtg gag gcc gtc aca ggg agg agc gcc atc ctg tcc ttc gtg ggc tac			353
Val Glu Ala Val Thr Gly Arg Ser Ala Ile Leu Ser Phe Val Gly Tyr			
	75	80	85
ggc tgc tac tgt ggg ctg ggg ggc cgt ggc cag ccc aag gat gag gtg			401
Gly Cys Tyr Cys Gly Leu Gly Gly Arg Gly Gln Pro Lys Asp Glu Val			
	90	95	100

gac tgg tgc tgc cac gcc cac gac tgc tgc tac cag gaa ctc ttt gac 449
 Asp Trp Cys Cys His Ala His Asp Cys Cys Tyr Gln Glu Leu Phe Asp
 105 110 115
 caa ggc tgt cac ccc tat gtg gac cac tat gat cac acc atc gag aac 497
 Gln Gly Cys His Pro Tyr Val Asp His Tyr Asp His Thr Ile Glu Asn
 120 125 130 135
 aac act gag ata gtc tgc agt gac ctc aac aag aca gag tgt gac aag 545
 Asn Thr Glu Ile Val Cys Ser Asp Leu Asn Lys Thr Glu Cys Asp Lys
 140 145 150
 cag aca tgc atg tgt gac aag aac atg gtt ctg tgc ctc atg aac cag 593
 Gln Thr Cys Met Cys Asp Lys Asn Met Val Leu Cys Leu Met Asn Gln
 155 160 165
 acg tac cga gag gag tac cgt ggc ttc ctc aat gtc tac tgc cag ggc 641
 Thr Tyr Arg Glu Glu Tyr Arg Gly Phe Leu Asn Val Tyr Cys Gln Gly
 170 175 180
 ccc acg ccc aac tgc agc atc tat gaa ccg ccc cct gag gag gtc acc 689
 Pro Thr Pro Asn Cys Ser Ile Tyr Glu Pro Pro Pro Glu Glu Val Thr
 185 190 195
 tgc agt cac caa tcc cca gcg ccc ccc gcc cct ccc tag agcctctgag 738
 Cys Ser His Gln Ser Pro Ala Pro Pro Ala Pro Pro *
 200 205 210

gtttgagaga gagagcgga ggagggtctg gcttggggac cagacgaggt gcagggaggg 798
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<211> 211

<212> PRT

<213> Homo Sapiens

<400> 23

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 20 25 30
 Cys Pro Ser Arg Thr Ser Arg Ser Ser Leu Gly Met Lys Lys Phe Phe
 35 40 45
 Thr Val Ala Ile Leu Ala Gly Ser Val Leu Ser Thr Ala His Gly Ser

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      50              55              60
Leu Leu Asn Leu Lys Ala Met Val Glu Ala Val Thr Gly Arg Ser Ala
65              70              75              80
Ile Leu Ser Phe Val Gly Tyr Gly Cys Tyr Cys Gly Leu Gly Gly Arg
      85              90              95
Gly Gln Pro Lys Asp Glu Val Asp Trp Cys Cys His Ala His Asp Cys
      100              105              110
Cys Tyr Gln Glu Leu Phe Asp Gln Gly Cys His Pro Tyr Val Asp His
      115              120              125
Tyr Asp His Thr Ile Glu Asn Asn Thr Glu Ile Val Cys Ser Asp Leu
      130              135              140
Asn Lys Thr Glu Cys Asp Lys Gln Thr Cys Met Cys Asp Lys Asn Met
145              150              155              160
Val Leu Cys Leu Met Asn Gln Thr Tyr Arg Glu Glu Tyr Arg Gly Phe
      165              170              175
Leu Asn Val Tyr Cys Gln Gly Pro Thr Pro Asn Cys Ser Ile Tyr Glu
      180              185              190
Pro Pro Pro Glu Glu Val Thr Cys Ser His Gln Ser Pro Ala Pro Pro
      195              200              205
Ala Pro Pro
      210

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Met Ala Asp Gly Ala Lys Ala Asn Pro Lys Gly Phe Lys Lys Lys Val
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ctg gat aga tgc ttc tct ggg tgg agg ggc cca cgc ttc ggg gcc tcc 96
Leu Asp Arg Cys Phe Ser Gly Trp Arg Gly Pro Arg Phe Gly Ala Ser
              20              25              30

tgt cct tca aga acc tcc agg tct agc ctg ggt atg aag aag ttc ttc 144
Cys Pro Ser Arg Thr Ser Arg Ser Ser Leu Gly Met Lys Lys Phe Phe
              35              40              45

acc gtg gcc atc ctt gct ggc agc gtt ctg tcc aca gct cac ggc agc 192
Thr Val Ala Ile Leu Ala Gly Ser Val Leu Ser Thr Ala His Gly Ser
              50              55              60

ctg ctc aac ctg aag gcc atg gtg gag gcc gtc aca ggg agg agc gcc 240
Leu Leu Asn Leu Lys Ala Met Val Glu Ala Val Thr Gly Arg Ser Ala
65              70              75              80

atc ctg tcc ttc gtg ggc tac ggt tgc tac tgt ggg ctg ggg ggc cgt 288
Ile Leu Ser Phe Val Gly Tyr Gly Cys Tyr Cys Gly Leu Gly Gly Arg
      85              90              95

ggc cag ccc aag gat gag gtg gac tgg tgc tgc cac gcc cac gac tgc 336
Gly Gln Pro Lys Asp Glu Val Asp Trp Cys Cys His Ala His Asp Cys
      100              105              110

tgc tac cag gaa ctc ttt gac caa ggc tgt cac ccc tat gtg gac cac 384
Cys Tyr Gln Glu Leu Phe Asp Gln Gly Cys His Pro Tyr Val Asp His
      115              120              125

tat gat cac acc atc gag aac aac act gag ata gtc tgc agt gac ctc 432
Tyr Asp His Thr Ile Glu Asn Asn Thr Glu Ile Val Cys Ser Asp Leu
      130              135              140

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aac aag aca gag tgt gac aag cag aca tgc atg tgt gac aag aac atg 480
Asn Lys Thr Glu Cys Asp Lys Gln Thr Cys Met Cys Asp Lys Asn Met
145 150 155 160

gtt ctg tgc ctc atg aac cag acg tac cga gag gag tac cgt ggc ttc 528
Val Leu Cys Leu Met Asn Gln Thr Tyr Arg Glu Glu Tyr Arg Gly Phe
165 170 175

ctc aat gtc tac tgc cag ggc ccc acg ccc aac tgc agc atc tat gaa 576
Leu Asn Val Tyr Cys Gln Gly Pro Thr Pro Asn Cys Ser Ile Tyr Glu
180 185 190

ccg ccc cct gag gag gtc acc tgc agt cac caa tcc cca gcg ccc ccc 624
Pro Pro Pro Glu Glu Val Thr Cys Ser His Gln Ser Pro Ala Pro Pro
195 200 205

gcc cct ccc tag 636
Ala Pro Pro *
210

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<211> 3486
<212> DNA
<213> Homo Sapiens

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Met Ala Lys Ile Asn
1 5

acc caa tac tcc cac ccc tcc agg acc cac ctc aag gta aag acc tca 102
Thr Gln Tyr Ser His Pro Ser Arg Thr His Leu Lys Val Lys Thr Ser
10 15 20

gac cga gat ctc aat cgc gct gaa aat ggc ctc agc aga gcc cac tcg 150
Asp Arg Asp Leu Asn Arg Ala Glu Asn Gly Leu Ser Arg Ala His Ser
25 30 35

tca agt gag gag aca tcg tca gtg ctg cag ccg ggg atc gcc atg gag 198
Ser Ser Glu Glu Thr Ser Ser Val Leu Gln Pro Gly Ile Ala Met Glu
40 45 50

acc aga gga ctg gct gac tcc ggg cag ggc tcc ttc acc ggc cag ggg 246
Thr Arg Gly Leu Ala Asp Ser Gly Gln Gly Ser Phe Thr Gly Gln Gly
55 60 65

atc gcc agg ctg tcg cgc ctc atc ttc ttg ctg cgc agg tgg gct gcc 294
Ile Ala Arg Leu Ser Arg Leu Ile Phe Leu Leu Arg Arg Trp Ala Ala
70 75 80 85

agg cat gtg cac cac cag gac cag gga ccg gac tct ttt cct gat cgt 342
Arg His Val His His Gln Asp Gln Gly Pro Asp Ser Phe Pro Asp Arg
90 95 100

ttc cgt gga gcc gag ctt aag gag gtg tcc agc caa gaa agc aat gcc 390
Phe Arg Gly Ala Glu Leu Lys Glu Val Ser Ser Gln Glu Ser Asn Ala
105 110 115

cag gca aat gtg ggc agc cag gag cca gca gac aga ggg aga agc gcc 438
Gln Ala Asn Val Gly Ser Gln Glu Pro Ala Asp Arg Gly Arg Ser Ala
120 125 130

tgg ccc ctg gcc aaa tgc aac act aac acc agc aac aac acg gag gag 486
Trp Pro Leu Ala Lys Cys Asn Thr Asn Thr Ser Asn Asn Thr Glu Glu

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135	140	145	
gag aag aag acg aaa aag aag gat gcg atc gtg gtg gac ccg tcc agc Glu Lys Lys Thr Lys Lys Lys Asp Ala Ile Val Val Asp Pro Ser Ser 150 155 160			534
aac ctg tac tac cgc tgg ctg acc gcc atc gcc ctg cct gtc ttc tat Asn Leu Tyr Tyr Arg Trp Leu Thr Ala Ile Ala Leu Pro Val Phe Tyr 170 175 180			582
aac tgg tat ctg ctt att tgc agg gcc tgt ttc gat gag ctg cag tcc Asn Trp Tyr Leu Leu Ile Cys Arg Ala Cys Phe Asp Glu Leu Gln Ser 185 190 195			630
gag tac ctg atg ctg tgg ctg gtc ctg gac tac tcg gca gat gtc ctg Glu Tyr Leu Met Leu Trp Leu Val Leu Asp Tyr Ser Ala Asp Val Leu 200 205 210			678
tat gtc ttg gat gtg ctt gta cga gct cgg aca ggt ttt ctc gag caa Tyr Val Leu Asp Val Leu Val Arg Ala Arg Thr Gly Phe Leu Glu Gln 215 220 225			726
ggc tta atg gtc agt gat acc aac agg ctg tgg cag cat tac aag acg Gly Leu Met Val Ser Asp Thr Asn Arg Leu Trp Gln His Tyr Lys Thr 230 235 240 245			774
acc acg cag ttc aag ctg gat gtg ttg tcc ctg gtc ccc acc gac ctg Thr Thr Gln Phe Lys Leu Asp Val Leu Ser Leu Val Pro Thr Asp Leu 250 255 260			822
gct tac tta aag gtg ggc aca aac tac cca gaa gtg agg ttc aac cgc Ala Tyr Leu Lys Val Gly Thr Asn Tyr Pro Glu Val Arg Phe Asn Arg 265 270 275			870
cta ctg aag ttt tcc cgg ctc ttt gaa ttc ttt gac cgc aca gag aca Leu Leu Lys Phe Ser Arg Leu Phe Glu Phe Phe Asp Arg Thr Glu Thr 280 285 290			918
agg acc aac tac ccc aat atg ttc agg att ggg aac ttg gtc ttg tac Arg Thr Asn Tyr Pro Asn Met Phe Arg Ile Gly Asn Leu Val Leu Tyr 295 300 305			966
att ctc atc atc atc cac tgg aat gcc tgc atc tac ttt gcc att tcc Ile Leu Ile Ile Ile His Trp Asn Ala Cys Ile Tyr Phe Ala Ile Ser 310 315 320 325			1014
aag ttc att ggt ttt ggg aca gac tcc tgg gtc tac cca aac atc tca Lys Phe Ile Gly Phe Gly Thr Asp Ser Trp Val Tyr Pro Asn Ile Ser 330 335 340			1062
atc cca gag cat ggg cgc ctc tcc agg aag tac att tac agt ctc tac Ile Pro Glu His Gly Arg Leu Ser Arg Lys Tyr Ile Tyr Ser Leu Tyr 345 350 355			1110
tgg tcc acc ttg acc ctt acc acc att ggt gag acc cca ccc ccc gtg Trp Ser Thr Leu Thr Leu Thr Thr Ile Gly Glu Thr Pro Pro Pro Val 360 365 370			1158
aaa gat gag gag tat ctc ttt gtg gtc gta gac ttc ttg gtg ggt gtt Lys Asp Glu Glu Tyr Leu Phe Val Val Val Asp Phe Leu Val Gly Val 375 380 385			1206
ctg att ttt gcc acc att gtg ggc aat gtg ggc tcc atg atc tcg aat Leu Ile Phe Ala Thr Ile Val Gly Asn Val Gly Ser Met Ile Ser Asn 390 395 400 405			1254
atg aat gcc tca cgg gca gag ttc cag gcc aag att gat tcc atc aag Met Asn Ala Ser Arg Ala Glu Phe Gln Ala Lys Ile Asp Ser Ile Lys 410 415 420			1302

cag tac atg Gln Tyr Met	cag ttc cgc aag gtc Gln Phe Arg Lys Val	acc aag gac ttg gag acg cgg gtt Thr Lys Asp Leu Glu Thr Arg Val	1350
	425	430 435	
atc cgg tgg ttt gac tac ctg tgg gcc aac aag aag acg gtg gat gag Ile Arg Trp Phe Asp Tyr Leu Trp Ala Asn Lys Lys Thr Val Asp Glu	440	445 450	1398
aag gag gtg ctc aag agc ctc cca gac aag ctg aag gct gag atc gcc Lys Glu Val Leu Lys Ser Leu Pro Asp Lys Leu Lys Ala Glu Ile Ala	455	460 465	1446
atc aac gtg cac ctg gac acg ctg aag aag gtt cgc atc ttc cag gac Ile Asn Val His Leu Asp Thr Leu Lys Lys Val Arg Ile Phe Gln Asp	470	475 480 485	1494
tgt gag gca ggg ctg ctg gtg gag ctg gtg ctg aag ctg cga ccc act Cys Glu Ala Gly Leu Leu Val Glu Leu Val Leu Lys Leu Arg Pro Thr	490	495 500	1542
gtg ttc agc cct ggg gat tat atc tgc aag aag gga gat att ggg aag Val Phe Ser Pro Gly Asp Tyr Ile Cys Lys Lys Gly Asp Ile Gly Lys	505	510 515	1590
gag atg tac atc atc aac gag ggc aag ctg gcc gtg gtg gct gat gat Glu Met Tyr Ile Ile Asn Glu Gly Lys Leu Ala Val Val Ala Asp Asp	520	525 530	1638
ggg gtc acc cag ttc gtg gtc ctc agc gat ggc agc tac ttc ggg gag Gly Val Thr Gln Phe Val Val Leu Ser Asp Gly Ser Tyr Phe Gly Glu	535	540 545	1686
atc agc att ctg aac atc aag ggg agc aag tgc ggg aac cgc agg acg Ile Ser Ile Leu Asn Ile Lys Gly Ser Lys Ser Gly Asn Arg Arg Thr	550	555 560 565	1734
gcc aac atc cgc agc att ggc tac tca gac ctg ttc tgc ctc tca aag Ala Asn Ile Arg Ser Ile Gly Tyr Ser Asp Leu Phe Cys Leu Ser Lys	570	575 580	1782
gac gat ctc atg gag gcc ctc acc gag tac ccc gaa gcc aag aag gcc Asp Asp Leu Met Glu Ala Leu Thr Glu Tyr Pro Glu Ala Lys Lys Ala	585	590 595	1830
ctg gag gag aaa gga cgg cag atc ctg atg aaa gac aac ctg atc gat Leu Glu Glu Lys Gly Arg Gln Ile Leu Met Lys Asp Asn Leu Ile Asp	600	605 610	1878
gag gag ctg gcc agg gcg ggc gcg gac ccc aag gac ctt gag gag aaa Glu Glu Leu Ala Arg Ala Gly Ala Asp Pro Lys Asp Leu Glu Glu Lys	615	620 625	1926
gtg gag cag ctg ggg tcc tcc ctg gac acc ctg cag acc agg ttt gca Val Glu Gln Leu Gly Ser Ser Leu Asp Thr Leu Gln Thr Arg Phe Ala	630	635 640 645	1974
cgc ctc ctg gct gag tac aac gcc acc cag atg aag atg aag cag cgt Arg Leu Leu Ala Glu Tyr Asn Ala Thr Gln Met Lys Met Lys Gln Arg	650	655 660	2022
ctc agc caa ctg gaa agc cag gtg aag ggt ggt ggg gac aag ccc ctg Leu Ser Gln Leu Glu Ser Gln Val Lys Gly Gly Gly Asp Lys Pro Leu	665	670 675	2070
gct gat ggg gaa gtt ccc ggg gat gct aca aaa aca gag gac aaa caa Ala Asp Gly Glu Val Pro Gly Asp Ala Thr Lys Thr Glu Asp Lys Gln	680	685 690	2118

cag tga aaatgcagca tctgtctcct gcttcacagg gtcgactgtc aggggtgaccg 2174
Gln *

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<211> 694

<212> PRT

<213> Homo Sapiens

<400> 26

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Lys	Val	Lys	Thr	Ser	Asp	Arg	Asp	Leu	Asn	Arg	Ala	Glu	Asn	Gly	Leu
			20					25					30		
Ser	Arg	Ala	His	Ser	Ser	Ser	Glu	Glu	Thr	Ser	Ser	Val	Leu	Gln	Pro
		35					40					45			
Gly	Ile	Ala	Met	Glu	Thr	Arg	Gly	Leu	Ala	Asp	Ser	Gly	Gln	Gly	Ser
	50					55					60				
Phe	Thr	Gly	Gln	Gly	Ile	Ala	Arg	Leu	Ser	Arg	Leu	Ile	Phe	Leu	Leu
	65				70					75				80	
Arg	Arg	Trp	Ala	Ala	Arg	His	Val	His	His	Gln	Asp	Gln	Gly	Pro	Asp
			85					90						95	
Ser	Phe	Pro	Asp	Arg	Phe	Arg	Gly	Ala	Glu	Leu	Lys	Glu	Val	Ser	Ser
			100					105					110		
Gln	Glu	Ser	Asn	Ala	Gln	Ala	Asn	Val	Gly	Ser	Gln	Glu	Pro	Ala	Asp
		115					120					125			
Arg	Gly	Arg	Ser	Ala	Trp	Pro	Leu	Ala	Lys	Cys	Asn	Thr	Asn	Thr	Ser
	130					135					140				
Asn	Asn	Thr	Glu	Glu	Glu	Lys	Lys	Thr	Lys	Lys	Lys	Asp	Ala	Ile	Val
	145				150					155				160	
Val	Asp	Pro	Ser	Ser	Asn	Leu	Tyr	Tyr	Arg	Trp	Leu	Thr	Ala	Ile	Ala
				165					170					175	
Leu	Pro	Val	Phe	Tyr	Asn	Trp	Tyr	Leu	Leu	Ile	Cys	Arg	Ala	Cys	Phe
			180					185					190		
Asp	Glu	Leu	Gln	Ser	Glu	Tyr	Leu	Met	Leu	Trp	Leu	Val	Leu	Asp	Tyr
	195						200					205			
Ser	Ala	Asp	Val	Leu	Tyr	Val	Leu	Asp	Val	Leu	Val	Arg	Ala	Arg	Thr
	210					215					220				
Gly	Phe	Leu	Glu	Gln	Gly	Leu	Met	Val	Ser	Asp	Thr	Asn	Arg	Leu	Trp
	225				230					235				240	
Gln	His	Tyr	Lys	Thr	Thr	Thr	Gln	Phe	Lys	Leu	Asp	Val	Leu	Ser	Leu
			245						250					255	
Val	Pro	Thr	Asp	Leu	Ala	Tyr	Leu	Lys	Val	Gly	Thr	Asn	Tyr	Pro	Glu
			260					265					270		
Val	Arg	Phe	Asn	Arg	Leu	Leu	Lys	Phe	Ser	Arg	Leu	Phe	Glu	Phe	Phe
	275						280					285			

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Asp Arg Thr Glu Thr Arg Thr Asn Tyr Pro Asn Met Phe Arg Ile Gly
290                295                300
Asn Leu Val Leu Tyr Ile Leu Ile Ile Ile His Trp Asn Ala Cys Ile
305                310                315                320
Tyr Phe Ala Ile Ser Lys Phe Ile Gly Phe Gly Thr Asp Ser Trp Val
325                330                335
Tyr Pro Asn Ile Ser Ile Pro Glu His Gly Arg Leu Ser Arg Lys Tyr
340                345                350
Ile Tyr Ser Leu Tyr Trp Ser Thr Leu Thr Leu Thr Thr Ile Gly Glu
355                360                365
Thr Pro Pro Pro Val Lys Asp Glu Glu Tyr Leu Phe Val Val Val Asp
370                375                380
Phe Leu Val Gly Val Leu Ile Phe Ala Thr Ile Val Gly Asn Val Gly
385                390                395                400
Ser Met Ile Ser Asn Met Asn Ala Ser Arg Ala Glu Phe Gln Ala Lys
405                410                415
Ile Asp Ser Ile Lys Gln Tyr Met Gln Phe Arg Lys Val Thr Lys Asp
420                425                430
Leu Glu Thr Arg Val Ile Arg Trp Phe Asp Tyr Leu Trp Ala Asn Lys
435                440                445
Lys Thr Val Asp Glu Lys Glu Val Leu Lys Ser Leu Pro Asp Lys Leu
450                455                460
Lys Ala Glu Ile Ala Ile Asn Val His Leu Asp Thr Leu Lys Lys Val
465                470                475                480
Arg Ile Phe Gln Asp Cys Glu Ala Gly Leu Leu Val Glu Leu Val Leu
485                490                495
Lys Leu Arg Pro Thr Val Phe Ser Pro Gly Asp Tyr Ile Cys Lys Lys
500                505                510
Gly Asp Ile Gly Lys Glu Met Tyr Ile Ile Asn Glu Gly Lys Leu Ala
515                520                525
Val Val Ala Asp Asp Gly Val Thr Gln Phe Val Val Leu Ser Asp Gly
530                535                540
Ser Tyr Phe Gly Glu Ile Ser Ile Leu Asn Ile Lys Gly Ser Lys Ser
545                550                555                560
Gly Asn Arg Arg Thr Ala Asn Ile Arg Ser Ile Gly Tyr Ser Asp Leu
565                570                575
Phe Cys Leu Ser Lys Asp Asp Leu Met Glu Ala Leu Thr Glu Tyr Pro
580                585                590
Glu Ala Lys Lys Ala Leu Glu Glu Lys Gly Arg Gln Ile Leu Met Lys
595                600                605
Asp Asn Leu Ile Asp Glu Glu Leu Ala Arg Ala Gly Ala Asp Pro Lys
610                615                620
Asp Leu Glu Glu Lys Val Glu Gln Leu Gly Ser Ser Leu Asp Thr Leu
625                630                635                640
Gln Thr Arg Phe Ala Arg Leu Leu Ala Glu Tyr Asn Ala Thr Gln Met
645                650                655
Lys Met Lys Gln Arg Leu Ser Gln Leu Glu Ser Gln Val Lys Gly Gly
660                665                670
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675                680                685
Thr Glu Asp Lys Gln Gln
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<210> 27
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 <212> DNA
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Lys	Val	Lys	Thr	Ser	Asp	Arg	Asp	Leu	Asn	Arg	Ala	Glu	Asn	Gly	Leu	
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agc	aga	gcc	cac	tgc	tca	agt	gag	gag	aca	tgc	tca	gtg	ctg	cag	ccg	144
Ser	Arg	Ala	His	Ser	Ser	Ser	Glu	Glu	Thr	Ser	Ser	Val	Leu	Gln	Pro	
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ggg	atc	gcc	atg	gag	acc	aga	gga	ctg	gct	gac	tcc	ggg	cag	ggc	tcc	192
Gly	Ile	Ala	Met	Glu	Thr	Arg	Gly	Leu	Ala	Asp	Ser	Gly	Gln	Gly	Ser	
	50					55					60					
ttc	acc	ggc	cag	ggg	atc	gcc	agg	ctg	tgc	cgc	ctc	atc	ttc	ttg	ctg	240
Phe	Thr	Gly	Gln	Gly	Ile	Ala	Arg	Leu	Ser	Arg	Leu	Ile	Phe	Leu	Leu	
	65				70					75					80	
cgc	agg	tgg	gct	gcc	agg	cat	gtg	cac	cac	cag	gac	cag	gga	ccg	gac	288
Arg	Arg	Trp	Ala	Ala	Arg	His	Val	His	His	Gln	Asp	Gln	Gly	Pro	Asp	
				85					90					95		
tct	ttt	cct	gat	cgt	ttc	cgt	gga	gcc	gag	ctt	aag	gag	gtg	tcc	agc	336
Ser	Phe	Pro	Asp	Arg	Phe	Arg	Gly	Ala	Glu	Leu	Lys	Glu	Val	Ser	Ser	
			100				105						110			
caa	gaa	agc	aat	gcc	cag	gca	aat	gtg	ggc	agc	cag	gag	cca	gca	gac	384
Gln	Glu	Ser	Asn	Ala	Gln	Ala	Asn	Val	Gly	Ser	Gln	Glu	Pro	Ala	Asp	
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aga	ggg	aga	agc	gcc	tgg	ccc	ctg	gcc	aaa	tgc	aac	act	aac	acc	agc	432
Arg	Gly	Arg	Ser	Ala	Trp	Pro	Leu	Ala	Lys	Cys	Asn	Thr	Asn	Thr	Ser	
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Val	Asp	Pro	Ser	Ser	Asn	Leu	Tyr	Tyr	Arg	Trp	Leu	Thr	Ala	Ile	Ala	
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ctg	cct	gtc	ttc	tat	aac	tgg	tat	ctg	ctt	att	tgc	agg	gcc	tgt	ttc	576
Leu	Pro	Val	Phe	Tyr	Asn	Trp	Tyr	Leu	Leu	Ile	Cys	Arg	Ala	Cys	Phe	
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gat	gag	ctg	cag	tcc	gag	tac	ctg	atg	ctg	tgg	ctg	gtc	ctg	gac	tac	624
Asp	Glu	Leu	Gln	Ser	Glu	Tyr	Leu	Met	Leu	Trp	Leu	Val	Leu	Asp	Tyr	
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Ser	Ala	Asp	Val	Leu	Tyr	Val	Leu	Asp	Val	Leu	Val	Arg	Ala	Arg	Thr	
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Gln	His	Tyr	Lys	Thr	Thr	Thr	Gln	Phe	Lys	Leu	Asp	Val	Leu	Ser	Leu	
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gtc	ccc	acc	gac	ctg	gct	tac	tta	aag	gtg	ggc	aca	aac	tac	cca	gaa	816
Val	Pro	Thr	Asp	Leu	Ala	Tyr	Leu	Lys	Val	Gly	Thr	Asn	Tyr	Pro	Glu	
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gtg	agg	ttc	aac	cgc	cta	ctg	aag	ttt	tcc	cgg	ctc	ttt	gaa	ttc	ttt	864
Val	Arg	Phe	Asn	Arg	Leu	Leu	Lys	Phe	Ser	Arg	Leu	Phe	Glu	Phe	Phe	
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gac	cgc	aca	gag	aca	agg	acc	aac	tac	ccc	aat	atg	ttc	agg	att	ggg	912
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att tac agt ctc tac tgg tcc acc ttg acc ctt acc acc att ggt gag Ile Tyr Ser Leu Tyr Trp Ser Thr Leu Thr Leu Thr Thr Ile Gly Glu 355 360 365			1104
acc cca ccc ccc gtg aaa gat gag gag tat ctc ttt gtg gtc gta gac Thr Pro Pro Pro Val Lys Asp Glu Glu Tyr Leu Phe Val Val Val Asp 370 375 380			1152
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 Phe Cys Leu Ser Lys Asp Asp Leu Met Glu Ala Leu Thr Glu Tyr Pro
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 Gln Thr Arg Phe Ala Arg Leu Leu Ala Glu Tyr Asn Ala Thr Gln Met
 645 650 655

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 Lys Met Lys Gln Arg Leu Ser Gln Leu Glu Ser Gln Val Lys Gly Gly
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 Met Thr Gln
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agg agc att gca ggt cct att tgc aac ctg aag ttt gtg act ctc ctg 165
 Arg Ser Ile Ala Gly Pro Ile Cys Asn Leu Lys Phe Val Thr Leu Leu
 5 10 15

gtt gcc tta agt tca gaa ctc cca ttc ctg gga gct gga gta cag ctt 213
 Val Ala Leu Ser Ser Glu Leu Pro Phe Leu Gly Ala Gly Val Gln Leu
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caa gac aat ggg tat aat gga ttg ctc att gca att aat cct cag gta 261
 Gln Asp Asn Gly Tyr Asn Gly Leu Leu Ile Ala Ile Asn Pro Gln Val
 40 45 50

cct gag aat cag aac ctc atc tca aac att aag gaa atg ata act gaa 309
 Pro Glu Asn Gln Asn Leu Ile Ser Ala Ile Lys Glu Met Ile Thr Glu
 55 60 65

gct tca ttt tac cta ttt aat gct acc aag aga aga gta ttt ttc aga 357
 Ala Ser Phe Tyr Leu Phe Asn Ala Thr Lys Arg Arg Val Phe Phe Arg
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ccc caa gaa aac tgt att att agt aag ctt ttt aaa gaa gga tgc acc Pro Gln Glu Asn Cys Ile Ile Ser Lys Leu Phe Lys Glu Gly Cys Thr 215 220 225	789
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Ser Lys Gly Glu Ile Arg Ala Gln Leu His Gln Ile Asn Ser Asn Asp	
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Asp Arg Lys Leu Leu Val Ser Tyr Leu Pro Thr Thr Val Ser Ala Lys	
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Thr Asp Ile Ser Ile Cys Ser Gly Leu Lys Lys Gly Phe Glu Val Val	
390 395 400	
gaa aaa ctg aat gga aaa gct tat ggc tct gtg atg ata tta gtg acc	1365
Glu Lys Leu Asn Gly Lys Ala Tyr Gly Ser Val Met Ile Leu Val Thr	
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Ser Gly Asp Asp Lys Leu Leu Gly Asn Cys Leu Pro Thr Val Leu Ser	
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Ser Gly Ser Thr Ile His Ser Ile Ala Leu Gly Ser Ser Ala Ala Pro	
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Asn Leu Glu Glu Leu Ser Arg Leu Thr Gly Gly Leu Lys Phe Phe Val	
455 460 465	
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485 490 495	
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Thr Gly Glu Asn Val Lys Pro His His Gln Leu Lys Asn Thr Val Thr	
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535 540 545	
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Tyr Tyr Thr Asn Asn Phe Ile Thr Asn Leu Thr Phe Arg Thr Ala Ser	
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Asn Asn Thr His His Ser Leu Gln Ala Leu Lys Val Thr Val Thr Ser	
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gaa aga gac agc ctc cat ttt cct cat cct gtg atg att tat gcc aat	1989
Glu Arg Asp Ser Leu His Phe Pro His Pro Val Met Ile Tyr Ala Asn	
615 620 625	
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Val Lys Gln Gly Phe Tyr Pro Ile Leu Asn Ala Thr Val Thr Ala Thr	

630	635	640	
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 920 925 930

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 35 40 45
 Pro Gln Val Pro Glu Asn Gln Asn Leu Ile Ser Asn Ile Lys Glu Met
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 Ile Thr Glu Ala Ser Phe Tyr Leu Phe Asn Ala Thr Lys Arg Arg Val
 65 70 75 80
 Phe Phe Arg Asn Ile Lys Ile Leu Ile Pro Ala Thr Trp Lys Ala Asn
 85 90 95
 Asn Asn Ser Lys Ile Lys Gln Glu Ser Tyr Glu Lys Ala Asn Val Ile
 100 105 110
 Val Thr Asp Trp Tyr Gly Ala His Gly Asp Asp Pro Tyr Thr Leu Gln
 115 120 125
 Tyr Arg Gly Cys Gly Lys Glu Gly Lys Tyr Ile His Phe Thr Pro Asn
 130 135 140
 Phe Leu Leu Asn Asp Asn Leu Thr Ala Gly Tyr Gly Ser Arg Gly Arg
 145 150 155 160
 Val Phe Val His Glu Trp Ala His Leu Arg Trp Gly Val Phe Asp Glu
 165 170 175
 Tyr Asn Asn Asp Lys Pro Phe Tyr Ile Asn Gly Gln Asn Gln Ile Lys
 180 185 190
 Val Thr Arg Cys Ser Ser Asp Ile Thr Gly Ile Phe Val Cys Glu Lys
 195 200 205
 Gly Pro Cys Pro Gln Glu Asn Cys Ile Ile Ser Lys Leu Phe Lys Glu
 210 215 220
 Gly Cys Thr Phe Ile Tyr Asn Ser Thr Gln Asn Ala Thr Ala Ser Ile
 225 230 235 240
 Met Phe Met Gln Ser Leu Ser Ser Val Val Glu Phe Cys Asn Ala Ser
 245 250 255
 Thr His Asn Gln Glu Ala Pro Asn Leu Gln Asn Gln Met Cys Ser Leu
 260 265 270
 Arg Ser Ala Trp Asp Val Ile Thr Asp Ser Ala Asp Phe His His Ser
 275 280 285
 Phe Pro Met Asn Gly Thr Glu Leu Pro Pro Pro Pro Thr Phe Ser Leu
 290 295 300
 Val Gln Ala Gly Asp Lys Val Val Cys Leu Val Leu Asp Val Ser Ser
 305 310 315 320
 Lys Met Ala Glu Ala Asp Arg Leu Leu Gln Leu Gln Gln Ala Ala Glu
 325 330 335
 Phe Tyr Leu Met Gln Ile Val Glu Ile His Thr Phe Val Gly Ile Ala
 340 345 350
 Ser Phe Asp Ser Lys Gly Glu Ile Arg Ala Gln Leu His Gln Ile Asn
 355 360 365
 Ser Asn Asp Asp Arg Lys Leu Leu Val Ser Tyr Leu Pro Thr Thr Val
 370 375 380
 Ser Ala Lys Thr Asp Ile Ser Ile Cys Ser Gly Leu Lys Lys Gly Phe
 385 390 395 400
 Glu Val Val Glu Lys Leu Asn Gly Lys Ala Tyr Gly Ser Val Met Ile
 405 410 415

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Val	Leu	Ser	Ser	Gly	Ser	Thr	Ile	His	Ser	Ile	Ala	Leu	Gly	Ser	Ser
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Ala	Ala	Pro	Asn	Leu	Glu	Glu	Leu	Ser	Arg	Leu	Thr	Gly	Gly	Leu	Lys
		450					455					460			
Phe	Phe	Val	Pro	Asp	Ile	Ser	Asn	Ser	Asn	Ser	Met	Ile	Asp	Ala	Phe
465					470						475				480
Ser	Arg	Ile	Ser	Ser	Gly	Thr	Gly	Asp	Ile	Phe	Gln	Gln	His	Ile	Gln
				485					490					495	
Leu	Glu	Ser	Thr	Gly	Glu	Asn	Val	Lys	Pro	His	His	Gln	Leu	Lys	Asn
			500					505					510		
Thr	Val	Thr	Val	Asp	Asn	Thr	Val	Gly	Asn	Asp	Thr	Met	Phe	Leu	Val
		515					520					525			
Thr	Trp	Gln	Ala	Ser	Gly	Pro	Pro	Glu	Ile	Ile	Leu	Phe	Asp	Pro	Asp
	530					535					540				
Gly	Arg	Lys	Tyr	Tyr	Thr	Asn	Asn	Phe	Ile	Thr	Asn	Leu	Thr	Phe	Arg
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Thr	Ala	Ser	Leu	Trp	Ile	Pro	Gly	Thr	Ala	Lys	Pro	Gly	His	Trp	Thr
			565						570					575	
Tyr	Thr	Leu	Asn	Asn	Thr	His	His	Ser	Leu	Gln	Ala	Leu	Lys	Val	Thr
			580					585					590		
Val	Thr	Ser	Arg	Ala	Ser	Asn	Ser	Ala	Val	Pro	Pro	Ala	Thr	Val	Glu
		595					600					605			
Ala	Phe	Val	Glu	Arg	Asp	Ser	Leu	His	Phe	Pro	His	Pro	Val	Met	Ile
	610					615					620				
Tyr	Ala	Asn	Val	Lys	Gln	Gly	Phe	Tyr	Pro	Ile	Leu	Asn	Ala	Thr	Val
625					630					635					640
Thr	Ala	Thr	Val	Glu	Pro	Glu	Thr	Gly	Asp	Pro	Val	Thr	Leu	Arg	Leu
			645						650					655	
Leu	Asp	Asp	Gly	Ala	Gly	Ala	Asp	Val	Ile	Lys	Asn	Asp	Gly	Ile	Tyr
			660					665					670		
Ser	Arg	Tyr	Phe	Phe	Ser	Phe	Ala	Ala	Asn	Gly	Arg	Tyr	Ser	Leu	Lys
		675					680					685			
Val	His	Val	Asn	His	Ser	Pro	Ser	Ile	Ser	Thr	Pro	Ala	His	Ser	Ile
	690					695					700				
Pro	Gly	Ser	His	Ala	Met	Tyr	Val	Pro	Gly	Tyr	Thr	Ala	Asn	Gly	Asn
705					710					715					720
Ile	Gln	Met	Asn	Ala	Pro	Arg	Lys	Ser	Val	Gly	Arg	Asn	Glu	Glu	Glu
			725						730					735	
Arg	Lys	Trp	Gly	Phe	Ser	Arg	Val	Ser	Ser	Gly	Gly	Ser	Phe	Ser	Val
		740						745					750		
Leu	Gly	Val	Pro	Ala	Gly	Pro	His	Pro	Asp	Val	Phe	Pro	Pro	Cys	Lys
		755					760					765			
Ile	Ile	Asp	Leu	Glu	Ala	Val	Lys	Val	Glu	Glu	Glu	Leu	Thr	Leu	Ser
	770					775					780				
Trp	Thr	Ala	Pro	Gly	Glu	Asp	Phe	Asp	Gln	Gly	Gln	Ala	Thr	Ser	Tyr
785					790					795					800
Glu	Ile	Arg	Met	Ser	Lys	Ser	Leu	Gln	Asn	Ile	Gln	Asp	Asp	Phe	Asn
			805						810					815	
Asn	Ala	Ile	Leu	Val	Asn	Thr	Ser	Lys	Arg	Asn	Pro	Gln	Gln	Ala	Gly
			820					825					830		
Ile	Arg	Glu	Ile	Phe	Thr	Phe	Ser	Pro	Gln	Ile	Ser	Thr	Asn	Gly	Pro
		835					840					845			
Glu	His	Gln	Pro	Asn	Gly	Glu	Thr	His	Glu	Ser	His	Arg	Ile	Tyr	Val
	850					855					860				
Ala	Ile	Arg	Ala	Met	Asp	Arg	Asn	Ser	Leu	Gln	Ser	Ala	Val	Ser	Asn
865					870					875					880
Ile	Ala	Gln	Ala	Pro	Leu	Phe	Ile	Pro	Pro	Asn	Ser	Asp	Pro	Val	Pro
			885						890					895	
Ala	Arg	Asp	Tyr	Leu	Ile	Leu	Lys	Gly	Val	Leu	Thr	Ala	Met	Gly	Leu
		900						905					910		
Ile	Gly	Ile	Ile	Cys	Leu	Ile	Ile	Val	Val	Thr	His	His	Thr	Leu	Ser
	915						920					925			
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 <213> Homo Sapiens

<220>
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 <222> (1)...(2832)

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 1 5 10 15
 act ctc ctg gtt gcc tta agt tca gaa ctc cca ttc ctg gga gct gga 96
 Thr Leu Leu Val Ala Leu Ser Ser Glu Leu Pro Phe Leu Gly Ala Gly
 20 25 30
 gta cag ctt caa gac aat ggg tat aat gga ttg ctc att gca att aat 144
 Val Gln Leu Gln Asp Asn Gly Tyr Asn Gly Leu Leu Ile Ala Ile Asn
 35 40 45
 cct cag gta cct gag aat cag aac ctc atc tca aac att aag gaa atg 192
 Pro Gln Val Pro Glu Asn Gln Asn Leu Ile Ser Asn Ile Lys Glu Met
 50 55 60
 ata act gaa gct tca ttt tac cta ttt aat gct acc aag aga aga gta 240
 Ile Thr Glu Ala Ser Phe Tyr Leu Phe Asn Ala Thr Lys Arg Arg Val
 65 70 75 80
 ttt ttc aga aat ata aag att tta ata cct gcc aca tgg aaa gct aat 288
 Phe Phe Arg Asn Ile Lys Ile Leu Ile Pro Ala Thr Trp Lys Ala Asn
 85 90 95
 aat aac agc aaa ata aaa caa gaa tca tat gaa aag gca aat gtc ata 336
 Asn Asn Ser Lys Ile Lys Gln Glu Ser Tyr Glu Lys Ala Asn Val Ile
 100 105 110
 gtg act gac tgg tat ggg gca cat gga gat gat cca tac acc cta caa 384
 Val Thr Asp Trp Tyr Gly Ala His Gly Asp Asp Pro Tyr Thr Leu Gln
 115 120 125
 tac aga ggg tgt gga aaa gag gga aaa tac att cat ttc aca cct aat 432
 Tyr Arg Gly Cys Gly Lys Glu Gly Lys Tyr Ile His Phe Thr Pro Asn
 130 135 140
 ttc cta ctg aat gat aac tta aca gct ggc tac gga tca cga ggc cga 480
 Phe Leu Leu Asn Asp Asn Leu Thr Ala Gly Tyr Gly Ser Arg Gly Arg
 145 150 155 160
 gtg ttt gtc cat gaa tgg gcc cac ctc cgt tgg ggt gtg ttc gat gag 528
 Val Phe Val His Glu Trp Ala His Leu Arg Trp Gly Val Phe Asp Glu
 165 170 175
 tat aac aat gac aaa cct ttc tac ata aat ggg caa aat caa att aaa 576
 Tyr Asn Asn Asp Lys Pro Phe Tyr Ile Asn Gly Gln Asn Gln Ile Lys
 180 185 190
 gtg aca agg tgt tca tct gac atc aca ggc att ttt gtg tgt gaa aaa 624
 Val Thr Arg Cys Ser Ser Asp Ile Thr Gly Ile Phe Val Cys Glu Lys
 195 200 205
 ggt cct tgc ccc caa gaa aac tgt att att agt aag ctt ttt aaa gaa 672
 Gly Pro Cys Pro Gln Glu Asn Cys Ile Ile Ser Lys Leu Phe Lys Glu
 210 215 220
 gga tgc acc ttt atc tac aat agc acc caa aat gca act gca tca ata 720
 Gly Cys Thr Phe Ile Tyr Asn Ser Thr Gln Asn Ala Thr Ala Ser Ile
 225 230 235 240

atg ttc atg caa agt tta tct tct gtg gtt gaa ttt tgt aat gca agt	768
Met Phe Met Gln Ser Leu Ser Ser Val Val Glu Phe Cys Asn Ala Ser	
245 250 255	
acc cac aac caa gaa gca cca aac cta cag aac cag atg tgc agc ctc	816
Thr His Asn Gln Glu Ala Pro Asn Leu Gln Asn Gln Met Cys Ser Leu	
260 265 270	
aga agt gca tgg gat gta atc aca gac tct gct gac ttt cac cac agc	864
Arg Ser Ala Trp Asp Val Ile Thr Asp Ser Ala Asp Phe His His Ser	
275 280 285	
ttt ccc atg aat ggg act gag ctt cca cct cct ccc aca ttc tcg ctt	912
Phe Pro Met Asn Gly Thr Glu Leu Pro Pro Pro Pro Thr Phe Ser Leu	
290 295 300	
gta cag gct ggt gac aaa gtg gtc tgt tta gtg ctg gat gtg tcc agc	960
Val Gln Ala Gly Asp Lys Val Val Cys Leu Val Leu Asp Val Ser Ser	
305 310 315 320	
aag atg gca gag gct gac aga ctc ctt caa cta caa caa gcc gca gaa	1008
Lys Met Ala Glu Ala Asp Arg Leu Leu Gln Leu Gln Ala Ala Glu	
325 330 335	
ttt tat ttg atg cag att gtt gaa att cat acc ttc gtg ggc att gcc	1056
Phe Tyr Leu Met Gln Ile Val Glu Ile His Thr Phe Val Gly Ile Ala	
340 345 350	
agt ttc gac agc aaa gga gag atc aga gcc cag cta cac caa att aac	1104
Ser Phe Asp Ser Lys Gly Glu Ile Arg Ala Gln Leu His Gln Ile Asn	
355 360 365	
agc aat gat gat cga aag ttg ctg gtt tca tat ctg ccc acc act gta	1152
Ser Asn Asp Asp Arg Lys Leu Leu Val Ser Tyr Leu Pro Thr Thr Val	
370 375 380	
tca gct aaa aca gac atc agc att tgt tca ggg ctt aag aaa gga ttt	1200
Ser Ala Lys Thr Asp Ile Ser Ile Cys Ser Gly Leu Lys Lys Gly Phe	
385 390 395 400	
gag gtg gtt gaa aaa ctg aat gga aaa gct tat ggc tct gtg atg ata	1248
Glu Val Val Glu Lys Leu Asn Gly Lys Ala Tyr Gly Ser Val Met Ile	
405 410 415	
tta gtg acc agc gga gat gat aag ctt ctt ggc aat tgc tta ccc act	1296
Leu Val Thr Ser Gly Asp Asp Lys Leu Leu Gly Asn Cys Leu Pro Thr	
420 425 430	
gtg ctc agc agt ggt tca aca att cac tcc att gcc ctg ggt tca tct	1344
Val Leu Ser Ser Gly Ser Thr Ile His Ser Ile Ala Leu Gly Ser Ser	
435 440 445	
gca gcc cca aat ctg gag gaa tta tca cgt ctt aca gga ggt tta aag	1392
Ala Ala Pro Asn Leu Glu Glu Leu Ser Arg Leu Thr Gly Gly Leu Lys	
450 455 460	
ttc ttt gtt cca gat ata tca aac tcc aat agc atg att gat gct ttc	1440
Phe Phe Val Pro Asp Ile Ser Asn Ser Asn Ser Met Ile Asp Ala Phe	
465 470 475 480	
agt aga att tcc tct gga act gga gac att ttc cag caa cat att cag	1488
Ser Arg Ile Ser Ser Gly Thr Gly Asp Ile Phe Gln Gln His Ile Gln	
485 490 495	
ctt gaa agt aca ggt gaa aat gtc aaa cct cac cat caa ttg aaa aac	1536
Leu Glu Ser Thr Gly Glu Asn Val Lys Pro His His Gln Leu Lys Asn	
500 505 510	
aca gtg act gtg gat aat act gtg ggc aac gac act atg ttt cta gtt	1584

Thr	Val	Thr	Val	Asp	Asn	Thr	Val	Gly	Asn	Asp	Thr	Met	Phe	Leu	Val	
	515						520					525				
acg	tgg	cag	gcc	agt	ggg	cct	cct	gag	att	ata	tta	ttt	gat	cct	gat	1632
Thr	Trp	Gln	Ala	Ser	Gly	Pro	Pro	Glu	Ile	Ile	Leu	Phe	Asp	Pro	Asp	
	530					535					540					
gga	cga	aaa	tac	tac	aca	aat	aat	ttt	atc	acc	aat	cta	act	ttt	cgg	1680
Gly	Arg	Lys	Tyr	Tyr		Asn	Asn	Phe	Ile		Asn	Leu	Thr	Phe	Arg	
545					550					555					560	
aca	gct	agt	ctt	tgg	att	cca	gga	aca	gct	aag	cct	ggg	cac	tgg	act	1728
Thr	Ala	Ser	Leu	Trp	Ile	Pro	Gly	Thr	Ala	Lys	Pro	Gly	His	Trp	Thr	
				565				570						575		
tac	acc	ctg	aac	aat	acc	cat	cat	tct	ctg	caa	gcc	ctg	aaa	gtg	aca	1776
Tyr	Thr	Leu	Asn	Asn	Thr	His	His	Ser	Leu	Gln	Ala	Leu	Lys	Val	Thr	
			580					585					590			
gtg	acc	tct	cgc	gcc	tcc	aac	tca	gct	gtg	ccc	cca	gcc	act	gtg	gaa	1824
Val	Thr	Ser	Arg	Ala	Ser	Asn	Ser	Ala	Val	Pro	Pro	Ala	Thr	Val	Glu	
		595					600					605				
gcc	ttt	gtg	gaa	aga	gac	agc	ctc	cat	ttt	cct	cat	cct	gtg	atg	att	1872
Ala	Phe	Val	Glu	Arg	Asp	Ser	Leu	His	Phe	Pro	His	Pro	Val	Met	Ile	
	610					615					620					
tat	gcc	aat	gtg	aaa	cag	gga	ttt	tat	ccc	att	ctt	aat	gcc	act	gtc	1920
Tyr	Ala	Asn	Val	Lys	Gln	Gly	Phe	Tyr	Pro	Ile	Leu	Asn	Ala	Thr	Val	
625					630					635					640	
act	gcc	aca	gtt	gag	cca	gag	act	gga	gat	cct	gtt	acg	ctg	aga	ctc	1968
Thr	Ala	Thr	Val	Glu	Pro	Glu	Thr	Gly	Asp	Pro	Val	Thr	Leu	Arg	Leu	
				645					650					655		
ctt	gat	gat	gga	gca	ggg	gct	gat	gtt	ata	aaa	aat	gat	gga	att	tac	2016
Leu	Asp	Asp	Gly	Ala	Gly	Ala	Asp	Val	Ile	Lys	Asn	Asp	Gly	Ile	Tyr	
			660					665					670			
tcg	agg	tat	ttt	ttc	tcc	ttt	gct	gca	aat	ggg	aga	tat	agc	ttg	aaa	2064
Ser	Arg	Tyr	Phe	Phe	Ser	Phe	Ala	Ala	Asn	Gly	Arg	Tyr	Ser	Leu	Lys	
		675					680					685				
gtg	cat	gtc	aat	cac	tct	ccc	agc	ata	agc	acc	cca	gcc	cac	tct	att	2112
Val	His	Val	Asn	His	Ser	Pro	Ser	Ile	Ser	Thr	Pro	Ala	His	Ser	Ile	
		690				695					700					
cca	ggg	agt	cat	gct	atg	tat	gta	cca	ggg	tac	aca	gca	aac	ggg	aat	2160
Pro	Gly	Ser	His	Ala	Met	Tyr	Val	Pro	Gly	Tyr	Thr	Ala	Asn	Gly	Asn	
705					710					715					720	
att	cag	atg	aat	gct	cca	agg	aaa	tca	gta	ggc	aga	aat	gag	gag	gag	2208
Ile	Gln	Met	Asn	Ala	Pro	Arg	Lys	Ser	Val	Gly	Arg	Asn	Glu	Glu	Glu	
				725					730					735		
cga	aag	tgg	ggc	ttt	agc	cga	gtc	agc	tca	gga	ggc	tcc	ttt	tca	gtg	2256
Arg	Lys	Trp	Gly	Phe	Ser	Arg	Val	Ser	Ser	Gly	Gly	Ser	Phe	Ser	Val	
			740					745					750			
ctg	gga	gtt	cca	gct	ggc	ccc	cac	cct	gat	gtg	ttt	cca	cca	tgc	aaa	2304
Leu	Gly	Val	Pro	Ala	Gly	Pro	His	Pro	Asp	Val	Phe	Pro	Pro	Cys	Lys	
		755					760					765				
att	att	gac	ctg	gaa	gct	gta	aaa	gta	gaa	gag	gaa	ttg	acc	cta	tct	2352
Ile	Ile	Asp	Leu	Glu	Ala	Val	Lys	Val	Glu	Glu	Glu	Leu	Thr	Leu	Ser	
		770				775					780					
tgg	aca	gca	cct	gga	gaa	gac	ttt	gat	cag	ggc	cag	gct	aca	agc	tat	2400
Trp	Thr	Ala	Pro	Gly	Glu	Asp	Phe	Asp	Gln	Gly	Gln	Ala	Thr	Ser	Tyr	

785	790	795	800	
gaa ata aga atg agt aaa agt cta cag aat atc caa gat gac ttt aac				2448
Glu Ile Arg Met Ser Lys Ser Leu Gln Asn Ile Gln Asp Asp Phe Asn	805	810	815	
aat gct att tta gta aat aca tca aag cga aat cct cag caa gct ggc				2496
Asn Ala Ile Leu Val Asn Thr Ser Lys Arg Asn Pro Gln Gln Ala Gly	820	825	830	
atc agg gag ata ttt acg ttc tca ccc cag att tcc acg aat gga cct				2544
Ile Arg Glu Ile Phe Thr Phe Ser Pro Gln Ile Ser Thr Asn Gly Pro	835	840	845	
gaa cat cag cca aat gga gaa aca cat gaa agc cac aga att tat gtt				2592
Glu His Gln Pro Asn Gly Glu Thr His Glu Ser His Arg Ile Tyr Val	850	855	860	
gca ata cga gca atg gat agg aac tcc tta cag tct gct gta tct aac				2640
Ala Ile Arg Ala Met Asp Arg Asn Ser Leu Gln Ser Ala Val Ser Asn	865	870	875	880
att gcc cag gcg cct ctg ttt att ccc ccc aat tct gat cct gta cct				2688
Ile Ala Gln Ala Pro Leu Phe Ile Pro Pro Asn Ser Asp Pro Val Pro	885	890	895	
gcc aga gat tat ctt ata ttg aaa gga gtt tta aca gca atg ggt ttg				2736
Ala Arg Asp Tyr Leu Ile Leu Lys Gly Val Leu Thr Ala Met Gly Leu	900	905	910	
ata gga atc att tgc ctt att ata gtt gtg aca cat cat act tta agc				2784
Ile Gly Ile Ile Cys Leu Ile Ile Val Val Thr His His Thr Leu Ser	915	920	925	
agg aaa aag aga gca gac aag aaa gag aat gga aca aaa tta tta taa				2832
Arg Lys Lys Arg Ala Asp Lys Lys Glu Asn Gly Thr Lys Leu Leu *	930	935	940	

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 <213> Homo Sapiens

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ttc ctc tta gtt ctg tgc ctg ctg cac cag tca aat act tcc ttc att				100
Phe Leu Leu Val Leu Cys Leu Leu His Gln Ser Asn Thr Ser Phe Ile	10	15	20	
aag ctg aat aat aat ggc ttt gaa gat att gtc att gtt ata gat cct				148
Lys Leu Asn Asn Asn Gly Phe Glu Asp Ile Val Ile Val Ile Asp Pro	25	30	35	40
agt gtg cca gaa gat gaa aaa ata att gaa caa ata gag gat atg gtg				196
Ser Val Pro Glu Asp Glu Lys Ile Ile Glu Gln Ile Glu Asp Met Val	45	50	55	
act aca gct tct acg tac ctg ttt gaa gcc aca gaa aaa aga ttt ttt				244
Thr Thr Ala Ser Thr Tyr Leu Phe Glu Ala Thr Glu Lys Arg Phe Phe	60	65	70	

ttc aaa aat gta tct ata tta att cct gag aat tgg aag gaa aat cct	292
Phe Lys Asn Val Ser Ile Leu Ile Pro Glu Asn Trp Lys Glu Asn Pro	
75 80 85	
cag tac aaa agg cca aaa cat gaa aac cat aaa cat gct gat gtt ata	340
Gln Tyr Lys Arg Pro Lys His Glu Asn His Lys His Ala Asp Val Ile	
90 95 100	
gtt gca cca cct aca ctc cca ggt aga gat gaa cca tac acc aag cag	388
Val Ala Pro Pro Thr Leu Pro Gly Arg Asp Glu Pro Tyr Thr Lys Gln	
105 110 115 120	
ttc aca gaa tgt gga gag aaa ggc gaa tac att cac ttc acc cct gac	436
Phe Thr Glu Cys Gly Glu Lys Gly Glu Tyr Ile His Phe Thr Pro Asp	
125 130 135	
ctt cta ctt gga aaa aaa caa aat gaa tat gga cca cca ggc aaa ctg	484
Leu Leu Leu Gly Lys Lys Gln Asn Glu Tyr Gly Pro Pro Gly Lys Leu	
140 145 150	
ttt gtc cat gag tgg gct cac ctc cgg tgg gga gtg ttt gat gag tac	532
Phe Val His Glu Trp Ala His Leu Arg Trp Gly Val Phe Asp Glu Tyr	
155 160 165	
aat gaa gat cag cct ttc tac cgt gct aag tca aaa aaa atc gaa gca	580
Asn Glu Asp Gln Pro Phe Tyr Arg Ala Lys Ser Lys Lys Ile Glu Ala	
170 175 180	
aca agg tgt tcc gca ggt atc tct ggt aga aat aga gtt tat aag tgt	628
Thr Arg Cys Ser Ala Gly Ile Ser Gly Arg Asn Arg Val Tyr Lys Cys	
185 190 195 200	
caa gga ggc agc tgt ctt agt aga gca tgc aga att gat tct aca aca	676
Gln Gly Gly Ser Cys Leu Ser Arg Ala Cys Arg Ile Asp Ser Thr Thr	
205 210 215	
aaa ctg tat gga aaa gat tgt caa ttc ttt cct gat aaa gta caa aca	724
Lys Leu Tyr Gly Lys Asp Cys Gln Phe Phe Pro Asp Lys Val Gln Thr	
220 225 230	
gaa aaa gca tcc ata atg ttt atg caa agt att gat tct gtt gtt gaa	772
Glu Lys Ala Ser Ile Met Phe Met Gln Ser Ile Asp Ser Val Val Glu	
235 240 245	
ttt tgt aac gaa aaa acc cat aat caa gaa gct cca agc cta caa aac	820
Phe Cys Asn Glu Lys Thr His Asn Gln Glu Ala Pro Ser Leu Gln Asn	
250 255 260	
ata aag tgc aat ttt aga agt aca tgg gag gtg att agc aat tct gag	868
Ile Lys Cys Asn Phe Arg Ser Thr Trp Glu Val Ile Ser Asn Ser Glu	
265 270 275 280	
gat ttt aaa aac acc ata ccc atg gtg aca cca cct cct cca cct gtc	916
Asp Phe Lys Asn Thr Ile Pro Met Val Thr Pro Pro Pro Pro Pro Val	
285 290 295	
ttc tca ttg ctg aag atc cgt caa aga att gtg tgc tta gtt ctt gat	964
Phe Ser Leu Leu Lys Ile Arg Gln Arg Ile Val Cys Leu Val Leu Asp	
300 305 310	
aag tct gga agc atg ggg ggt aag gac cgc cta aat cga atg aat caa	1012
Lys Ser Gly Ser Met Gly Gly Lys Asp Arg Leu Asn Arg Met Asn Gln	
315 320 325	
gca gca aaa cat ttc ctg ctg cag act gtt gaa aat gga tcc tgg gtg	1060
Ala Ala Lys His Phe Leu Leu Gln Thr Val Glu Asn Gly Ser Trp Val	
330 335 340	

ggg atg gtt cac ttt gat agt act gcc act att gta aat aag cta atc Gly Met Val His Phe Asp Ser Thr Ala Thr Ile Val Asn Lys Leu Ile 345 350 355 360	1108
caa ata aaa agc agt gat gaa aga aac aca ctc atg gca gga tta cct Gln Ile Lys Ser Ser Asp Glu Arg Asn Thr Leu Met Ala Gly Leu Pro 365 370 375	1156
aca tat cct ctg gga gga act tcc atc tgc tct gga att aaa tat gca Thr Tyr Pro Leu Gly Gly Thr Ser Ile Cys Ser Gly Ile Lys Tyr Ala 380 385 390	1204
ttt cag gtg att gga gag cta cat tcc caa ctc gat gga tcc gaa gta Phe Gln Val Ile Gly Glu Leu His Ser Gln Leu Asp Gly Ser Glu Val 395 400 405	1252
ctg ctg ctg act gat ggg gag gat aac act gca agt tct tgt att gat Leu Leu Leu Thr Asp Gly Glu Asp Asn Thr Ala Ser Ser Cys Ile Asp 410 415 420	1300
gaa gtg aaa caa agt ggg gcc att gtt cat ttt att gct ttg gga aga Glu Val Lys Gln Ser Gly Ala Ile Val His Phe Ile Ala Leu Gly Arg 425 430 435 440	1348
gct gct gat gaa gca gta ata gag atg agc aag ata aca gga gga agt Ala Ala Asp Glu Ala Val Ile Glu Met Ser Lys Ile Thr Gly Gly Ser 445 450 455	1396
cat ttt tat gtt tca gat gaa gct cag aac aat ggc ctc att gat gct His Phe Tyr Val Ser Asp Glu Ala Gln Asn Asn Gly Leu Ile Asp Ala 460 465 470	1444
ttt ggg gct ctt aca tca gga aat act gat ctc tcc cag aag tcc ctt Phe Gly Ala Leu Thr Ser Gly Asn Thr Asp Leu Ser Gln Lys Ser Leu 475 480 485	1492
cag ctc gaa agt aag gga tta aca ctg aat agt aat gcc tgg atg aac Gln Leu Glu Ser Lys Gly Leu Thr Leu Asn Ser Asn Ala Trp Met Asn 490 495 500	1540
gac act gtc ata att gat agt aca gtg gga aag gac acg ttc ttt ctc Asp Thr Val Ile Ile Asp Ser Thr Val Gly Lys Asp Thr Phe Phe Leu 505 510 515 520	1588
atc aca tgg aac agt ctg cct ccc agt att tct ctc tgg gat ccc agt Ile Thr Trp Asn Ser Leu Pro Pro Ser Ile Ser Leu Trp Asp Pro Ser 525 530 535	1636
gga aca ata atg gaa aat ttc aca gtg gat gca act tcc aaa atg gcc Gly Thr Ile Met Glu Asn Phe Thr Val Asp Ala Thr Ser Lys Met Ala 540 545 550	1684
tat ctc agt att cca gga act gca aag gtg ggc act tgg gca tac aat Tyr Leu Ser Ile Pro Gly Thr Ala Lys Val Gly Thr Trp Ala Tyr Asn 555 560 565	1732
ctt caa gcc aaa gcg aac cca gaa aca tta act att aca gta act tct Leu Gln Ala Lys Ala Asn Pro Glu Thr Leu Thr Ile Thr Val Thr Ser 570 575 580	1780
cga gca gca aat tct tct gtg cct cca atc aca gtg aat gct aaa atg Arg Ala Ala Asn Ser Ser Val Pro Pro Ile Thr Val Asn Ala Lys Met 585 590 595 600	1828
aat aag gac gta aac agt ttc ccc agc cca atg att gtt tac gca gaa Asn Lys Asp Val Asn Ser Phe Pro Ser Pro Met Ile Val Tyr Ala Glu 605 610 615	1876
att cta caa gga tat gta cct gtt ctt gga gcc aat gtg act gct ttc	1924

Ile	Leu	Gln	Gly	Tyr	Val	Pro	Val	Leu	Gly	Ala	Asn	Val	Thr	Ala	Phe	
			620					625					630			
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Ile	Glu	Ser	Gln	Asn	Gly	His	Thr	Glu	Val	Leu	Glu	Leu	Leu	Asp	Asn	
		635					640					645				
ggt	gca	ggc	gct	gat	tct	ttc	aag	aat	gat	gga	gtc	tac	tcc	agg	tat	2020
Gly	Ala	Gly	Ala	Asp	Ser	Phe	Lys	Asn	Asp	Gly	Val	Tyr	Ser	Arg	Tyr	
		650				655					660					
ttt	aca	gca	tat	aca	gaa	aat	ggc	aga	tat	agc	tta	aaa	gtt	cgg	gct	2068
Phe	Thr	Ala	Tyr	Thr	Glu	Asn	Gly	Arg	Tyr	Ser	Leu	Lys	Val	Arg	Ala	
					670					675					680	
cat	gga	gga	gca	aac	act	gcc	agg	cta	aaa	tta	cgg	cct	cca	ctg	aat	2116
His	Gly	Gly	Ala	Asn	Thr	Ala	Arg	Leu	Lys	Leu	Arg	Pro	Pro	Leu	Asn	
				685					690					695		
aga	gcc	gcg	tac	ata	cca	ggc	tgg	gta	gtg	aac	ggg	gaa	att	gaa	gca	2164
Arg	Ala	Ala	Tyr	Ile	Pro	Gly	Trp	Val	Val	Asn	Gly	Glu	Ile	Glu	Ala	
			700				705						710			
aac	ccg	cca	aga	cct	gaa	att	gat	gag	gat	act	cag	acc	acc	ttg	gag	2212
Asn	Pro	Pro	Arg	Pro	Glu	Ile	Asp	Glu	Asp	Thr	Gln	Thr	Thr	Leu	Glu	
		715					720					725				
gat	ttc	agc	cga	aca	gca	tcc	gga	ggt	gca	ttt	gtg	gta	tca	caa	gtc	2260
Asp	Phe	Ser	Arg	Thr	Ala	Ser	Gly	Gly	Ala	Phe	Val	Val	Ser	Gln	Val	
		730				735					740					
cca	agc	ctt	ccc	ttg	cct	gac	caa	tac	cca	cca	agt	caa	atc	aca	gac	2308
Pro	Ser	Leu	Pro	Leu	Pro	Asp	Gln	Tyr	Pro	Pro	Ser	Gln	Ile	Thr	Asp	
		745			750					755					760	
ctt	gat	gcc	aca	gtt	cat	gag	gat	aag	att	att	ctt	aca	tgg	aca	gca	2356
Leu	Asp	Ala	Thr	Val	His	Glu	Asp	Lys	Ile	Ile	Leu	Thr	Trp	Thr	Ala	
				765					770					775		
cca	gga	gat	aat	ttt	gat	gtt	gga	aaa	gtt	caa	cgt	tat	atc	ata	aga	2404
Pro	Gly	Asp	Asn	Phe	Asp	Val	Gly	Lys	Val	Gln	Arg	Tyr	Ile	Ile	Arg	
			780					785					790			
ata	agt	gca	agt	att	ctt	gat	cta	aga	gac	agt	ttt	gat	gat	gct	ctt	2452
Ile	Ser	Ala	Ser	Ile	Leu	Asp	Leu	Arg	Asp	Ser	Phe	Asp	Asp	Ala	Leu	
		795					800					805				
caa	gta	aat	act	act	gat	ctg	tca	cca	aag	gag	gcc	aac	tcc	aag	gaa	2500
Gln	Val	Asn	Thr	Thr	Asp	Leu	Ser	Pro	Lys	Glu	Ala	Asn	Ser	Lys	Glu	
		810				815					820					
agc	ttt	gca	ttt	aaa	cca	gaa	aat	atc	tca	gaa	gaa	aat	gca	acc	cac	2548
Ser	Phe	Ala	Phe	Lys	Pro	Glu	Asn	Ile	Ser	Glu	Glu	Asn	Ala	Thr	His	
		825			830					835				840		
ata	ttt	att	gcc	att	aaa	agt	ata	gat	aaa	agc	aat	ttg	aca	tca	aaa	2596
Ile	Phe	Ile	Ala	Ile	Lys	Ser	Ile	Asp	Lys	Ser	Asn	Leu	Thr	Ser	Lys	
				845					850					855		
gta	tcc	aac	att	gca	caa	gta	act	ttg	ttt	atc	cct	caa	gca	aat	cct	2644
Val	Ser	Asn	Ile	Ala	Gln	Val	Thr	Leu	Phe	Ile	Pro	Gln	Ala	Asn	Pro	
			860					865					870			
gat	gac	att	gat	cct	act	cct	act	cct	act	cct	act	cct	gat	aaa	agt	2692
Asp	Asp	Ile	Asp	Pro	Thr	Pro	Thr	Pro	Thr	Pro	Thr	Pro	Asp	Lys	Ser	
		875					880					885				
cat	aat	tct	gga	gtt	aat	att	tct	acg	ctg	gta	ttg	tct	gtg	att	ggg	2740
His	Asn	Ser	Gly	Val	Asn	Ile	Ser	Thr	Leu	Val	Leu	Ser	Val	Ile	Gly	

890 895 900

tct gtt gta att gtt aac ttt att tta agt acc acc att tga 2782
 Ser Val Val Ile Val Asn Phe Ile Leu Ser Thr Thr Ile *
 905 910 915

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 20 25 30
 Asp Ile Val Ile Val Ile Asp Pro Ser Val Pro Glu Asp Glu Lys Ile
 35 40 45
 Ile Glu Gln Ile Glu Asp Met Val Thr Thr Ala Ser Thr Tyr Leu Phe
 50 55 60
 Glu Ala Thr Glu Lys Arg Phe Phe Phe Lys Asn Val Ser Ile Leu Ile
 65 70 75 80
 Pro Glu Asn Trp Lys Glu Asn Pro Gln Tyr Lys Arg Pro Lys His Glu
 85 90 95
 Asn His Lys His Ala Asp Val Ile Val Ala Pro Pro Thr Leu Pro Gly
 100 105 110
 Arg Asp Glu Pro Tyr Thr Lys Gln Phe Thr Glu Cys Gly Glu Lys Gly
 115 120 125
 Glu Tyr Ile His Phe Thr Pro Asp Leu Leu Leu Gly Lys Lys Gln Asn
 130 135 140
 Glu Tyr Gly Pro Pro Gly Lys Leu Phe Val His Glu Trp Ala His Leu
 145 150 155 160
 Arg Trp Gly Val Phe Asp Glu Tyr Asn Glu Asp Gln Pro Phe Tyr Arg
 165 170 175
 Ala Lys Ser Lys Lys Ile Glu Ala Thr Arg Cys Ser Ala Gly Ile Ser
 180 185 190
 Gly Arg Asn Arg Val Tyr Lys Cys Gln Gly Gly Ser Cys Leu Ser Arg
 195 200 205
 Ala Cys Arg Ile Asp Ser Thr Thr Lys Leu Tyr Gly Lys Asp Cys Gln
 210 215 220
 Phe Phe Pro Asp Lys Val Gln Thr Glu Lys Ala Ser Ile Met Phe Met
 225 230 235 240
 Gln Ser Ile Asp Ser Val Val Glu Phe Cys Asn Glu Lys Thr His Asn
 245 250 255
 Gln Glu Ala Pro Ser Leu Gln Asn Ile Lys Cys Asn Phe Arg Ser Thr
 260 265 270
 Trp Glu Val Ile Ser Asn Ser Glu Asp Phe Lys Asn Thr Ile Pro Met
 275 280 285
 Val Thr Pro Pro Pro Pro Val Phe Ser Leu Leu Lys Ile Arg Gln
 290 295 300
 Arg Ile Val Cys Leu Val Leu Asp Lys Ser Gly Ser Met Gly Gly Lys
 305 310 315 320
 Asp Arg Leu Asn Arg Met Asn Gln Ala Lys His Phe Leu Leu Gln
 325 330 335
 Thr Val Glu Asn Gly Ser Trp Val Gly Met Val His Phe Asp Ser Thr
 340 345 350
 Ala Thr Ile Val Asn Lys Leu Ile Gln Ile Lys Ser Ser Asp Glu Arg
 355 360 365
 Asn Thr Leu Met Ala Gly Leu Pro Thr Tyr Pro Leu Gly Gly Thr Ser
 370 375 380

Ile	Cys	Ser	Gly	Ile	Lys	Tyr	Ala	Phe	Gln	Val	Ile	Gly	Glu	Leu	His
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Ser	Gln	Leu	Asp	Gly	Ser	Glu	Val	Leu	Leu	Leu	Thr	Asp	Gly	Glu	Asp
				405					410					415	
Asn	Thr	Ala	Ser	Ser	Cys	Ile	Asp	Glu	Val	Lys	Gln	Ser	Gly	Ala	Ile
			420					425					430		
Val	His	Phe	Ile	Ala	Leu	Gly	Arg	Ala	Ala	Asp	Glu	Ala	Val	Ile	Glu
		435					440					445			
Met	Ser	Lys	Ile	Thr	Gly	Gly	Ser	His	Phe	Tyr	Val	Ser	Asp	Glu	Ala
	450				455						460				
Gln	Asn	Asn	Gly	Leu	Ile	Asp	Ala	Phe	Gly	Ala	Leu	Thr	Ser	Gly	Asn
465				470						475					480
Thr	Asp	Leu	Ser	Gln	Lys	Ser	Leu	Gln	Leu	Glu	Ser	Lys	Gly	Leu	Thr
				485					490					495	
Leu	Asn	Ser	Asn	Ala	Trp	Met	Asn	Asp	Thr	Val	Ile	Ile	Asp	Ser	Thr
			500					505					510		
Val	Gly	Lys	Asp	Thr	Phe	Phe	Leu	Ile	Thr	Trp	Asn	Ser	Leu	Pro	Pro
		515					520					525			
Ser	Ile	Ser	Leu	Trp	Asp	Pro	Ser	Gly	Thr	Ile	Met	Glu	Asn	Phe	Thr
	530					535					540				
Val	Asp	Ala	Thr	Ser	Lys	Met	Ala	Tyr	Leu	Ser	Ile	Pro	Gly	Thr	Ala
545					550					555					560
Lys	Val	Gly	Thr	Trp	Ala	Tyr	Asn	Leu	Gln	Ala	Lys	Ala	Asn	Pro	Glu
				565					570					575	
Thr	Leu	Thr	Ile	Thr	Val	Thr	Ser	Arg	Ala	Ala	Asn	Ser	Ser	Val	Pro
			580					585						590	
Pro	Ile	Thr	Val	Asn	Ala	Lys	Met	Asn	Lys	Asp	Val	Asn	Ser	Phe	Pro
		595					600					605			
Ser	Pro	Met	Ile	Val	Tyr	Ala	Glu	Ile	Leu	Gln	Gly	Tyr	Val	Pro	Val
	610					615					620				
Leu	Gly	Ala	Asn	Val	Thr	Ala	Phe	Ile	Glu	Ser	Gln	Asn	Gly	His	Thr
625				630						635					640
Glu	Val	Leu	Glu	Leu	Leu	Asp	Asn	Gly	Ala	Gly	Ala	Asp	Ser	Phe	Lys
				645					650					655	
Asn	Asp	Gly	Val	Tyr	Ser	Arg	Tyr	Phe	Thr	Ala	Tyr	Thr	Glu	Asn	Gly
			660					665					670		
Arg	Tyr	Ser	Leu	Lys	Val	Arg	Ala	His	Gly	Gly	Ala	Asn	Thr	Ala	Arg
		675					680					685			
Leu	Lys	Leu	Arg	Pro	Pro	Leu	Asn	Arg	Ala	Ala	Tyr	Ile	Pro	Gly	Trp
	690					695					700				
Val	Val	Asn	Gly	Glu	Ile	Glu	Ala	Asn	Pro	Pro	Arg	Pro	Glu	Ile	Asp
705				710						715					720
Glu	Asp	Thr	Gln	Thr	Leu	Glu	Asp	Phe	Ser	Arg	Thr	Ala	Ser	Gly	
				725				730					735		
Gly	Ala	Phe	Val	Val	Ser	Gln	Val	Pro	Ser	Leu	Pro	Leu	Pro	Asp	Gln
			740					745				750			
Tyr	Pro	Pro	Ser	Gln	Ile	Thr	Asp	Leu	Asp	Ala	Thr	Val	His	Glu	Asp
		755					760					765			
Lys	Ile	Ile	Leu	Thr	Trp	Thr	Ala	Pro	Gly	Asp	Asn	Phe	Asp	Val	Gly
	770					775					780				
Lys	Val	Gln	Arg	Tyr	Ile	Ile	Arg	Ile	Ser	Ala	Ser	Ile	Leu	Asp	Leu
785				790						795					800
Arg	Asp	Ser	Phe	Asp	Asp	Ala	Leu	Gln	Val	Asn	Thr	Thr	Asp	Leu	Ser
			805						810					815	
Pro	Lys	Glu	Ala	Asn	Ser	Lys	Glu	Ser	Phe	Ala	Phe	Lys	Pro	Glu	Asn
			820					825					830		
Ile	Ser	Glu	Glu	Asn	Ala	Thr	His	Ile	Phe	Ile	Ala	Ile	Lys	Ser	Ile
		835					840					845			
Asp	Lys	Ser	Asn	Leu	Thr	Ser	Lys	Val	Ser	Asn	Ile	Ala	Gln	Val	Thr
	850					855					860				
Leu	Phe	Ile	Pro	Gln	Ala	Asn	Pro	Asp	Asp	Ile	Asp	Pro	Thr	Pro	Thr
865				870						875					880
Pro	Thr	Pro	Thr	Pro	Asp	Lys	Ser	His	Asn	Ser	Gly	Val	Asn	Ile	Ser
				885					890					895	
Thr	Leu	Val	Leu	Ser	Val	Ile	Gly	Ser	Val	Val	Ile	Val	Asn	Phe	Ile
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 1 5 10 15

cac cag tca aat act tcc ttc att aag ctg aat aat aat ggc ttt gaa 96
 His Gln Ser Asn Thr Ser Phe Ile Lys Leu Asn Asn Asn Gly Phe Glu
 20 25 30

gat att gtc att gtt ata gat cct agt gtg cca gaa gat gaa aaa ata 144
 Asp Ile Val Ile Val Ile Asp Pro Ser Val Pro Glu Asp Glu Lys Ile
 35 40 45

att gaa caa ata gag gat atg gtg act aca gct tct acg tac ctg ttt 192
 Ile Glu Gln Ile Glu Asp Met Val Thr Thr Ala Ser Thr Tyr Leu Phe
 50 55 60

gaa gcc aca gaa aaa aga ttt ttt ttc aaa aat gta tct ata tta att 240
 Glu Ala Thr Glu Lys Arg Phe Phe Phe Lys Asn Val Ser Ile Leu Ile
 65 70 75 80

cct gag aat tgg aag gaa aat cct cag tac aaa agg cca aaa cat gaa 288
 Pro Glu Asn Trp Lys Glu Asn Pro Gln Tyr Lys Arg Pro Lys His Glu
 85 90 95

aac cat aaa cat gct gat gtt ata gtt gca cca cct aca ctc cca ggt 336
 Asn His Lys His Ala Asp Val Ile Val Ala Pro Pro Thr Leu Pro Gly
 100 105 110

aga gat gaa cca tac acc aag cag ttc aca gaa tgt gga gag aaa ggc 384
 Arg Asp Glu Pro Tyr Thr Lys Gln Phe Thr Glu Cys Gly Glu Lys Gly
 115 120 125

gaa tac att cac ttc acc cct gac ctt cta ctt gga aaa aaa caa aat 432
 Glu Tyr Ile His Phe Thr Pro Asp Leu Leu Leu Gly Lys Lys Gln Asn
 130 135 140

gaa tat gga cca cca ggc aaa ctg ttt gtc cat gag tgg gct cac ctc 480
 Glu Tyr Gly Pro Pro Gly Lys Leu Phe Val His Glu Trp Ala His Leu
 145 150 155 160

cgg tgg gga gtg ttt gat gag tac aat gaa gat cag cct ttc tac cgt 528
 Arg Trp Gly Val Phe Asp Glu Tyr Asn Glu Asp Gln Pro Phe Tyr Arg
 165 170 175

gct aag tca aaa aaa atc gaa gca aca agg tgt tcc gca ggt atc tct 576
 Ala Lys Ser Lys Lys Ile Glu Ala Thr Arg Cys Ser Ala Gly Ile Ser
 180 185 190

ggg aga aat aga gtt tat aag tgt caa gga ggc agc tgt ctt agt aga 624
 Gly Arg Asn Arg Val Tyr Lys Cys Gln Gly Gly Ser Cys Leu Ser Arg
 195 200 205

gca tgc aga att gat tct aca aca aaa ctg tat gga aaa gat tgt caa 672
 Ala Cys Arg Ile Asp Ser Thr Thr Lys Leu Tyr Gly Lys Asp Cys Gln
 210 215 220

ttc ttt cct gat aaa gta caa aca gaa aaa gca tcc ata atg ttt atg 720
 Phe Phe Pro Asp Lys Val Gln Thr Glu Lys Ala Ser Ile Met Phe Met

225	230	235	240	
caa agt att gat tct gtt gtt gaa ttt tgt aac gaa aaa acc cat aat				768
Gln Ser Ile Asp Ser Val Val Glu Phe Cys Asn Glu Lys Thr His Asn	245	250	255	
caa gaa gct cca agc cta caa aac ata aag tgc aat ttt aga agt aca				816
Gln Glu Ala Pro Ser Leu Gln Asn Ile Lys Cys Asn Phe Arg Ser Thr	260	265	270	
tgg gag gtg att agc aat tct gag gat ttt aaa aac acc ata ccc atg				864
Trp Glu Val Ile Ser Asn Ser Glu Asp Phe Lys Asn Thr Ile Pro Met	275	280	285	
gtg aca cca cct cct cca cct gtc ttc tca ttg ctg aag atc cgt caa				912
Val Thr Pro Pro Pro Pro Pro Val Phe Ser Leu Leu Lys Ile Arg Gln	290	295	300	
aga att gtg tgc tta gtt ctt gat aag tct gga agc atg ggg ggt aag				960
Arg Ile Val Cys Leu Val Leu Asp Lys Ser Gly Ser Met Gly Gly Lys	305	310	315	320
gac cgc cta aat cga atg aat caa gca gca aaa cat ttc ctg ctg cag				1008
Asp Arg Leu Asn Arg Met Asn Gln Ala Ala Lys His Phe Leu Leu Gln	325	330	335	
act gtt gaa aat gga tcc tgg gtg ggg atg gtt cac ttt gat agt act				1056
Thr Val Glu Asn Gly Ser Trp Val Gly Met Val His Phe Asp Ser Thr	340	345	350	
gcc act att gta aat aag cta atc caa ata aaa agc agt gat gaa aga				1104
Ala Thr Ile Val Asn Lys Leu Ile Gln Ile Lys Ser Ser Asp Glu Arg	355	360	365	
aac aca ctc atg gca gga tta cct aca tat cct ctg gga gga act tcc				1152
Asn Thr Leu Met Ala Gly Leu Pro Thr Tyr Pro Leu Gly Gly Thr Ser	370	375	380	
atc tgc tct gga att aaa tat gca ttt cag gtg att gga gag cta cat				1200
Ile Cys Ser Gly Ile Lys Tyr Ala Phe Gln Val Ile Gly Glu Leu His	385	390	395	400
tcc caa ctc gat gga tcc gaa gta ctg ctg ctg act gat ggg gag gat				1248
Ser Gln Leu Asp Gly Ser Glu Val Leu Leu Thr Asp Gly Glu Asp	405	410	415	
aac act gca agt tct tgt att gat gaa gtg aaa caa agt ggg gcc att				1296
Asn Thr Ala Ser Cys Ile Asp Glu Val Lys Gln Ser Gly Ala Ile	420	425	430	
gtt cat ttt att gct ttg gga aga gct gct gat gaa gca gta ata gag				1344
Val His Phe Ile Ala Leu Gly Arg Ala Ala Asp Glu Ala Val Ile Glu	435	440	445	
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Met Ser Lys Ile Thr Gly Ser His Phe Tyr Val Ser Asp Glu Ala	450	455	460	
cag aac aat ggc ctc att gat gct ttt ggg gct ctt aca tca gga aat				1440
Gln Asn Asn Gly Leu Ile Asp Ala Phe Gly Ala Leu Thr Ser Gly Asn	465	470	475	480
act gat ctc tcc cag aag tcc ctt cag ctc gaa agt aag gga tta aca				1488
Thr Asp Leu Ser Gln Lys Ser Leu Gln Leu Glu Ser Lys Gly Leu Thr	485	490	495	
ctg aat agt aat gcc tgg atg aac gac act gtc ata att gat agt aca				1536
Leu Asn Ser Asn Ala Trp Met Asn Asp Thr Val Ile Ile Asp Ser Thr	500	505	510	

gtg gga aag gac acg ttc ttt ctc atc aca tgg aac agt ctg cct ccc	1584
Val Gly Lys Asp Thr Phe Phe Leu Ile Thr Trp Asn Ser Leu Pro Pro	
515 520 525	
agt att tct ctc tgg gat ccc agt gga aca ata atg gaa aat ttc aca	1632
Ser Ile Ser Leu Trp Asp Pro Ser Gly Thr Ile Met Glu Asn Phe Thr	
530 535 540	
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Val Asp Ala Thr Ser Lys Met Ala Tyr Leu Ser Ile Pro Gly Thr Ala	
545 550 555 560	
aag gtg ggc act tgg gca tac aat ctt caa gcc aaa gcg aac cca gaa	1728
Lys Val Gly Thr Trp Ala Tyr Asn Leu Gln Ala Lys Ala Asn Pro Glu	
565 570 575	
aca tta act att aca gta act tct cga gca gca aat tct tct gtg cct	1776
Thr Leu Thr Ile Thr Val Thr Ser Arg Ala Ala Asn Ser Ser Val Pro	
580 585 590	
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Pro Ile Thr Val Asn Ala Lys Met Asn Lys Asp Val Asn Ser Phe Pro	
595 600 605	
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Ser Pro Met Ile Val Tyr Ala Glu Ile Leu Gln Gly Tyr Val Pro Val	
610 615 620	
ctt gga gcc aat gtg act gct ttc att gaa tca cag aat gga cat aca	1920
Leu Gly Ala Asn Val Thr Ala Phe Ile Glu Ser Gln Asn Gly His Thr	
625 630 635 640	
gaa gtt ttg gaa ctt ttg gat aat ggt gca ggc gct gat tct ttc aag	1968
Glu Val Leu Glu Leu Leu Asp Asn Gly Ala Gly Ala Asp Ser Phe Lys	
645 650 655	
aat gat gga gtc tac tcc agg tat ttt aca gca tat aca gaa aat ggc	2016
Asn Asp Gly Val Tyr Ser Arg Tyr Phe Thr Ala Tyr Thr Glu Asn Gly	
660 665 670	
aga tat agc tta aaa gtt cgg gct cat gga gga gca aac act gcc agg	2064
Arg Tyr Ser Leu Lys Val Arg Ala His Gly Gly Ala Asn Thr Ala Arg	
675 680 685	
cta aaa tta cgg cct cca ctg aat aga gcc gcg tac ata cca ggc tgg	2112
Leu Lys Leu Arg Pro Pro Leu Asn Arg Ala Ala Tyr Ile Pro Gly Trp	
690 695 700	
gta gtg aac ggg gaa att gaa gca aac ccg cca aga cct gaa att gat	2160
Val Val Asn Gly Glu Ile Glu Ala Asn Pro Pro Arg Pro Glu Ile Asp	
705 710 715 720	
gag gat act cag acc acc ttg gag gat ttc agc cga aca gca tcc gga	2208
Glu Asp Thr Gln Thr Thr Leu Glu Asp Phe Ser Arg Thr Ala Ser Gly	
725 730 735	
ggt gca ttt gtg gta tca caa gtc cca agc ctt ccc ttg cct gac caa	2256
Gly Ala Phe Val Val Ser Gln Val Pro Ser Leu Pro Leu Pro Asp Gln	
740 745 750	
tac cca cca agt caa atc aca gac ctt gat gcc aca gtt cat gag gat	2304
Tyr Pro Pro Ser Gln Ile Thr Asp Leu Asp Ala Thr Val His Glu Asp	
755 760 765	
aag att att ctt aca tgg aca gca cca gga gat aat ttt gat gtt gga	2352
Lys Ile Ile Leu Thr Trp Thr Ala Pro Gly Asp Asn Phe Asp Val Gly	
770 775 780	


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aaa gtt caa cgt tat atc ata aga ata agt gca agt att ctt gat cta 2400
Lys Val Gln Arg Tyr Ile Ile Arg Ile Ser Ala Ser Ile Leu Asp Leu
785 790 795 800

aga gac agt ttt gat gat gct ctt caa gta aat act act gat ctg tca 2448
Arg Asp Ser Phe Asp Asp Ala Leu Gln Val Asn Thr Thr Asp Leu Ser
805 810 815

cca aag gag gcc aac tcc aag gaa agc ttt gca ttt aaa cca gaa aat 2496
Pro Lys Glu Ala Asn Ser Lys Glu Ser Phe Ala Phe Lys Pro Glu Asn
820 825 830

atc tca gaa gaa aat gca acc cac ata ttt att gcc att aaa agt ata 2544
Ile Ser Glu Glu Asn Ala Thr His Ile Phe Ile Ala Ile Lys Ser Ile
835 840 845

gat aaa agc aat ttg aca tca aaa gta tcc aac att gca caa gta act 2592
Asp Lys Ser Asn Leu Thr Ser Lys Val Ser Asn Ile Ala Gln Val Thr
850 855 860

ttg ttt atc cct caa gca aat cct gat gac att gat cct act cct act 2640
Leu Phe Ile Pro Gln Ala Asn Pro Asp Asp Ile Asp Pro Thr Pro Thr
865 870 875 880

cct act cct act cct gat aaa agt cat aat tct gga gtt aat att tct 2688
Pro Thr Pro Thr Pro Asp Lys Ser His Asn Ser Gly Val Asn Ile Ser
885 890 895

acg ctg gta ttg tct gtg att ggg tct gtt gta att gtt aac ttt att 2736
Thr Leu Val Leu Ser Val Ile Gly Ser Val Val Ile Val Asn Phe Ile
900 905 910

tta agt acc acc att tga 2754
Leu Ser Thr Thr Ile *
915

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<210> 34
 <211> 1170
 <212> DNA
 <213> Homo Sapiens

<220>
 <221> CDS
 <222> (1)...(1170)

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<400> 34
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Met Gly Phe Met Asp Asp Asn Ala Thr Asn Thr Ser Thr Ser Phe Leu
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tct gtg ctc aac cct cat gga gcc cat gcc act tcc ttc cca ttc aac 96
Ser Val Leu Asn Pro His Gly Ala His Ala Thr Ser Phe Pro Phe Asn
20 25 30

ttc agc tac agc gac tat gat atg cct ttg gat gaa gat gag gat gtg 144
Phe Ser Tyr Ser Asp Tyr Asp Met Pro Leu Asp Glu Asp Glu Asp Val
35 40 45

acc aat tcc agg acg ttc ttt gct gcc aag att gtc att ggg atg gcc 192
Thr Asn Ser Arg Thr Phe Phe Ala Ala Lys Ile Val Ile Gly Met Ala
50 55 60

ctg gtg ggc atc atg ctg gtc tgc ggc att gga aac ttc atc ttt atc 240
Leu Val Gly Ile Met Leu Val Cys Gly Ile Gly Asn Phe Ile Phe Ile
65 70 75 80

gct gcc ctg gtc cgc tac aag aaa ctg cgc aac ctc acc aac ctg ctc 288
Ala Ala Leu Val Arg Tyr Lys Lys Leu Arg Asn Leu Thr Asn Leu Leu

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85										90										95									
atc	gcc	aac	ctg	gcc	atc	tct	gac	ttc	ctg	gtg	gcc	att	gtc	tgc	tgc					336									
Ile	Ala	Asn	Leu	Ala	Ile	Ser	Asp	Phe	Leu	Val	Ala	Ile	Val	Cys	Cys														
			100					105					110																
ccc	ttt	gag	atg	gac	tac	tat	gtg	gtg	cgc	cag	ctc	tcc	tgg	gag	cac					384									
Pro	Phe	Glu	Met	Asp	Tyr	Tyr	Val	Val	Arg	Gln	Leu	Ser	Trp	Glu	His														
			115				120					125																	
ggc	cac	gtc	ctg	tgc	acc	tct	gtc	aac	tac	ctg	cgc	act	gtc	tct	ctc					432									
Gly	His	Val	Leu	Cys	Thr		Val	Asn	Tyr	Leu	Arg	Thr	Val	Ser	Leu														
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tat	gtc	tcc	acc	aat	gcc	ctg	ctg	gcc	atc	gcc	att	gac	agg	tat	ctg					480									
Tyr	Val	Ser	Thr	Asn	Ala	Leu	Leu	Ala	Ile	Ala	Ile	Asp	Arg	Tyr	Leu														
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gct	att	gtc	cat	ccg	ctg	aga	cca	cgg	atg	aag	tgc	caa	aca	gcc	act					528									
Ala	Ile	Val	His		Pro	Leu	Arg	Pro	Arg	Met	Lys	Cys	Gln	Thr	Ala	Thr													
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ggc	ctg	att	gcc	tgg	gtg	tgg	acg	gtg	tcc	atc	ctg	atc	gcc	atc	cct					576									
Gly	Leu	Ile	Ala	Leu	Val	Trp	Thr	Val	Ser	Ile	Leu	Ile	Ala	Ile	Pro														
			180				185						190																
tcc	gcc	tac	ttc	acc	acc	gag	acg	gtc	ctc	gtc	att	gtc	aag	agc	cag					624									
Ser	Ala	Tyr	Phe	Thr	Thr	Glu	Thr	Val	Leu	Val	Ile	Val	Lys	Ser	Gln														
			195			200						205																	
gaa	aag	atc	ttc	tgc	ggc	cag	atc	tgg	cct	gtg	gac	cag	cag	ctc	tac					672									
Glu	Lys	Ile	Phe	Cys	Gly	Gln	Ile	Trp	Pro	Val	Asp	Gln	Gln	Leu	Tyr														
			210			215					220																		
tac	aag	tcc	tac	ttc	ctc	ttt	atc	ttt	ggc	ata	gaa	ttc	gtg	ggc	ccc					720									
Tyr	Lys	Ser	Tyr	Phe	Leu	Phe	Ile	Phe	Gly	Ile	Glu	Phe	Val	Gly	Pro														
					230				235					240															
gtg	gtc	acc	atg	acc	ctg	tgc	tat	gcc	agg	atc	tcc	cgg	gag	ctc	tgg					768									
Val	Val	Thr	Met	Thr	Leu	Cys	Tyr	Ala	Arg	Ile	Ser	Arg	Glu	Leu	Trp														
				245				250					255																
ttc	aag	gcg	gtc	cct	gga	ttc	cag	aca	gag	cag	atc	cgc	aag	agg	ctg					816									
Phe	Lys	Ala	Val	Pro	Gly	Phe	Gln	Thr	Glu	Gln	Ile	Arg	Lys	Arg	Leu														
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cgc	tgc	cgc	agg	aag	acg	gtc	ctg	gtg	ctc	atg	tgc	atc	ctc	acc	gcc					864									
Arg	Cys	Arg	Arg	Lys	Thr	Val	Leu	Val	Leu	Met	Cys	Ile	Leu	Thr	Ala														
			275				280					285																	
tac	gtg	cta	tgc	tgg	gcg	ccc	ttc	tac	ggc	ttc	acc	atc	gtg	cgc	gac					912									
Tyr	Val	Leu	Cys	Trp	Ala	Pro	Phe	Tyr	Gly	Phe	Thr	Ile	Val	Arg	Asp														
			290			295					300																		
ttc	ttc	ccc	acc	gtg	ttt	gtg	aag	gag	aag	cac	tac	ctc	act	gcc	ttc					960									
Phe	Phe	Pro	Thr	Val	Phe	Val	Lys	Glu	Lys	His	Tyr	Leu	Thr	Ala	Phe														
			305			310				315				320															
tac	atc	gtc	gag	tgc	atc	gcc	atg	agc	aac	agc	atg	atc	aac	act	ctg					1008									
Tyr	Ile	Val	Glu	Cys	Ile	Ala	Met	Ser	Asn	Ser	Met	Ile	Asn	Thr	Leu														
				325				330					335																
tgc	ttc	gtg	acc	gtc	aag	aac	gac	acc	gtc	aag	tac	ttc	aaa	aag	atc					1056									
Cys	Phe	Val	Thr	Val	Lys	Asn	Asp	Thr	Val	Lys	Tyr	Phe	Lys	Lys	Ile														
			340				345						350																
atg	ttg	ctc	cac	tgg	aac	gct	tct	tac	aat	ggc	ggt	aag	tcc	agt	gca					1104									
Met	Leu	Leu	His	Trp	Asn	Ala	Ser	Tyr	Asn	Gly	Gly	Lys	Ser	Ser	Ala														
			355				360					365																	

gac ctg gac ctc aag aca att ggg atg cct gcc acc gaa gag gtg gac 1152
 Asp Leu Asp Leu Lys Thr Ile Gly Met Pro Ala Thr Glu Glu Val Asp
 370 375 380

tgc atc aga cta aaa taa 1170
 Cys Ile Arg Leu Lys *
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<210> 35
 <211> 389
 <212> PRT
 <213> Homo Sapiens

<400> 35
 Met Gly Phe Met Asp Asn Ala Thr Asn Thr Ser Thr Ser Phe Leu
 1 5 10 15
 Ser Val Leu Asn Pro His Gly Ala His Ala Thr Ser Phe Pro Phe Asn
 20 25 30
 Phe Ser Tyr Ser Asp Tyr Asp Met Pro Leu Asp Glu Asp Glu Asp Val
 35 40 45
 Thr Asn Ser Arg Thr Phe Phe Ala Ala Lys Ile Val Ile Gly Met Ala
 50 55 60
 Leu Val Gly Ile Met Leu Val Cys Gly Ile Gly Asn Phe Ile Phe Ile
 65 70 75 80
 Ala Ala Leu Val Arg Tyr Lys Lys Leu Arg Asn Leu Thr Asn Leu Leu
 85 90 95
 Ile Ala Asn Leu Ala Ile Ser Asp Phe Leu Val Ala Ile Val Cys Cys
 100 105 110
 Pro Phe Glu Met Asp Tyr Tyr Val Val Arg Gln Leu Ser Trp Glu His
 115 120 125
 Gly His Val Leu Cys Thr Ser Val Asn Tyr Leu Arg Thr Val Ser Leu
 130 135 140
 Tyr Val Ser Thr Asn Ala Leu Leu Ala Ile Ala Ile Asp Arg Tyr Leu
 145 150 155 160
 Ala Ile Val His Pro Leu Arg Pro Arg Met Lys Cys Gln Thr Ala Thr
 165 170 175
 Gly Leu Ile Ala Leu Val Trp Thr Val Ser Ile Leu Ile Ala Ile Pro
 180 185 190
 Ser Ala Tyr Phe Thr Thr Glu Thr Val Leu Val Ile Val Lys Ser Gln
 195 200 205
 Glu Lys Ile Phe Cys Gly Gln Ile Trp Pro Val Asp Gln Gln Leu Tyr
 210 215 220
 Tyr Lys Ser Tyr Phe Leu Phe Ile Phe Gly Ile Glu Phe Val Gly Pro
 225 230 235 240
 Val Val Thr Met Thr Leu Cys Tyr Ala Arg Ile Ser Arg Glu Leu Trp
 245 250 255
 Phe Lys Ala Val Pro Gly Phe Gln Thr Glu Gln Ile Arg Lys Arg Leu
 260 265 270
 Arg Cys Arg Arg Lys Thr Val Leu Val Leu Met Cys Ile Leu Thr Ala
 275 280 285
 Tyr Val Leu Cys Trp Ala Pro Phe Tyr Gly Phe Thr Ile Val Arg Asp
 290 295 300
 Phe Phe Pro Thr Val Phe Val Lys Glu Lys His Tyr Leu Thr Ala Phe
 305 310 315 320
 Tyr Ile Val Glu Cys Ile Ala Met Ser Asn Ser Met Ile Asn Thr Leu
 325 330 335
 Cys Phe Val Thr Val Lys Asn Asp Thr Val Lys Tyr Phe Lys Lys Ile
 340 345 350
 Met Leu Leu His Trp Asn Ala Ser Tyr Asn Gly Gly Lys Ser Ser Ala
 355 360 365
 Asp Leu Asp Leu Lys Thr Ile Gly Met Pro Ala Thr Glu Glu Val Asp
 370 375 380
 Cys Ile Arg Leu Lys
 385

<210> 36

<211> 1170
 <212> DNA
 <213> Homo Sapiens

<220>
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 <222> (1)...(1170)

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 Met Gly Phe Met Asp Asp Asn Ala Thr Asn Thr Ser Thr Ser Phe Leu
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 tct gtg ctc aac cct cat gga gcc cat gcc act tcc ttc cca ttc aac 96
 Ser Val Leu Asn Pro His Gly Ala His Ala Thr Ser Phe Pro Phe Asn
 20 25 30
 ttc agc tac agc gac tat gat atg cct ttg gat gaa gat gag gat gtg 144
 Phe Ser Tyr Ser Asp Tyr Asp Met Pro Leu Asp Glu Asp Glu Asp Val
 35 40 45
 acc aat tcc agg acg ttc ttt gct gcc aag att gtc att ggg atg gcc 192
 Thr Asn Ser Arg Thr Phe Phe Ala Ala Lys Ile Val Ile Gly Met Ala
 50 55 60
 ctg gtg ggc atc atg ctg gtc tgc ggc att gga aac ttc atc ttt atc 240
 Leu Val Gly Ile Met Leu Val Cys Gly Ile Gly Asn Phe Ile Phe Ile
 65 70 75 80
 gct gcc ctg gtc cgc tac aag aaa ctg cgc aac ctc acc aac ctg ctc 288
 Ala Ala Leu Val Arg Tyr Lys Lys Leu Arg Asn Leu Thr Asn Leu Leu
 85 90 95
 atc gcc aac ctg gcc atc tct gac ttc ctg gtg gcc att gtc tgc tgc 336
 Ile Ala Asn Leu Ala Ile Ser Asp Phe Leu Val Ala Ile Val Cys Cys
 100 105 110
 ccc ttt gag atg gac tac tat gtg gtg cgc cag ctc tcc tgg gag cac 384
 Pro Phe Glu Met Asp Tyr Tyr Val Val Arg Gln Leu Ser Trp Glu His
 115 120 125
 ggc cac gtc ctg tgc acc tct gtc aac tac ctg cgc act gtc tct ctc 432
 Gly His Val Leu Cys Thr Ser Val Asn Tyr Leu Arg Thr Val Ser Leu
 130 135 140
 tat gtc tcc acc aat gcc ctg ctg gcc atc gcc att gac agg tat ctg 480
 Tyr Val Ser Thr Asn Ala Leu Leu Ala Ile Ala Ile Asp Arg Tyr Leu
 145 150 155 160
 gct att gtc cat ccg ctg aga cca cgg atg aag tgc caa aca gcc act 528
 Ala Ile Val His Pro Leu Arg Pro Arg Met Lys Cys Gln Thr Ala Thr
 165 170 175
 ggc ctg att gcc ttg gtg tgg acg gtg tcc atc ctg atc gcc atc cct 576
 Gly Leu Ile Ala Leu Val Trp Thr Val Ser Ile Leu Ile Ala Ile Pro
 180 185 190
 tcc gcc tac ttc acc acc gag acg gtc ctc gtc att gtc aag agc cag 624
 Ser Ala Tyr Phe Thr Thr Glu Thr Val Leu Val Ile Val Lys Ser Gln
 195 200 205
 gaa aag atc ttc tgc ggc cag atc tgg cct gtg gac cag cag ctc tac 672
 Glu Lys Ile Phe Cys Gly Gln Ile Trp Pro Val Asp Gln Gln Leu Tyr
 210 215 220
 tac aag tcc tac ttc ctc ttt atc ttt ggc ata gaa ttc gtg ggc ccc 720
 Tyr Lys Ser Tyr Phe Leu Phe Ile Phe Gly Ile Glu Phe Val Gly Pro
 225 230 235 240

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gtg gtc acc atg acc ctg tgc tat gcc agg atc tcc cgg gag ctc tgg 768
Val Val Thr Met Thr Leu Cys Tyr Ala Arg Ile Ser Arg Glu Leu Trp
                245                250                255

ttc aag gcg gtc cct gga ttc cag aca gag cag atc cgc aag agg ctg 816
Phe Lys Ala Val Pro Gly Phe Gln Thr Glu Gln Ile Arg Lys Arg Leu
                260                265                270

cgc tgc cgc agg aag acg gtc ctg gtg ctc atg tgc atc ctc acc gcc 864
Arg Cys Arg Arg Lys Thr Val Leu Val Leu Met Cys Ile Leu Thr Ala
                275                280                285

tac gtg cta tgc tgg gcg ccc ttc tac ggc ttc acc atc gtg cgc gac 912
Tyr Val Leu Cys Trp Ala Pro Phe Tyr Gly Phe Thr Ile Val Arg Asp
                290                295                300

ttc ttc ccc acc gtg ttt gtg aag gag aag cac tac ctc act gcc ttc 960
Phe Phe Pro Thr Val Phe Val Lys Glu Lys His Tyr Leu Thr Ala Phe
305                310                315                320

tac atc gtc gag tgc atc gcc atg agc aac agc atg atc aac act ctg 1008
Tyr Ile Val Glu Cys Ile Ala Met Ser Asn Ser Met Ile Asn Thr Leu
                325                330                335

tgc ttc gtg acc gtc aag aac gac acc gtc aag tac ttc aaa aag atc 1056
Cys Phe Val Thr Val Lys Asn Asp Thr Val Lys Tyr Phe Lys Lys Ile
                340                345                350

atg ttg ctc cac tgg aac gct tct tac aat ggc ggt aag tcc agt gca 1104
Met Leu Leu His Trp Asn Ala Ser Tyr Asn Gly Gly Lys Ser Ser Ala
                355                360                365

gac ctg gac ctc aag aca att ggg atg cct gcc acc gaa gag gtg gac 1152
Asp Leu Asp Leu Lys Thr Ile Gly Met Pro Ala Thr Glu Glu Val Asp
                370                375                380

tgc atc aga cta aaa taa 1170
Cys Ile Arg Leu Lys *
385

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<210> 37
<211> 1159
<212> DNA
<213> Homo Sapiens

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<220>
<221> CDS
<222> (64)...(1137)

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<400> 37
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gag atg gat tta cca gtg aac cta acc tcc ttt tcc ctc tcc acc ccc 108
Met Asp Leu Pro Val Asn Leu Thr Ser Phe Ser Leu Ser Thr Pro
1 5 10 15

tcc cct ttg gag acc aac cac agc ctc ggc aaa gac gac ctg cgc ccc 156
Ser Pro Leu Glu Thr Asn His Ser Leu Gly Lys Asp Asp Leu Arg Pro
20 25 30

agc tcg ccc ctg ctc tcg gtc ttc gga gtg ctt att ctc acc ttg ctg 204
Ser Ser Pro Leu Leu Ser Val Phe Gly Val Leu Ile Leu Thr Leu Leu
35 40 45

ggc ttt ctg gtg gcg gcg acg ttc gcc tgg aac ctg ctg gtg ctg gcg 252
Gly Phe Leu Val Ala Ala Thr Phe Ala Trp Asn Leu Leu Val Leu Ala
50 55 60

acc atc ctc cgt gta cgc acc ttc cac cgc gtg ccc cac aac ctg gtg 300

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Thr	Ile	Leu	Arg	Val	Arg	Thr	Phe	His	Arg	Val	Pro	His	Asn	Leu	Val		
65						70					75						
gca	tcc	atg	gcc	gtc	tcg	gat	gtc	ctg	gtg	gcc	gcg	ctg	gtc	atg	ccg	348	
Ala	Ser	Met	Ala	Val	Ser	Asp	Val	Leu	Val	Ala	Ala	Leu	Val	Met	Pro	95	
80					85					90							
ctg	agc	ctg	gtg	cat	gag	ctg	tcc	ggg	cgc	cgc	tgg	cag	cta	ggg	cgg	396	
Leu	Ser	Leu	Val	His	Glu	Leu	Ser	Gly	Arg	Arg	Trp	Gln	Leu	Gly	Arg	110	
				100					105								
agg	ctg	tgc	cag	ctt	tgg	atc	gcg	tgc	gac	gtg	ctt	tgc	tgc	acg	gcc	444	
Arg	Leu	Cys	Gln	Leu	Trp	Ile	Ala	Cys	Asp	Val	Leu	Cys	Cys	Thr	Ala	125	
			115					120									
agc	atc	tgg	aac	gtg	acg	gcc	ata	gcc	ctg	gac	cgc	tac	tgg	tcc	atc	492	
Ser	Ile	Trp	Asn	Val	Thr	Ala	Ile	Ala	Leu	Asp	Arg	Tyr	Trp	Ser	Ile	140	
		130					135										
acg	cgc	cac	atg	gaa	tac	acg	ctc	cgc	acc	cgc	aag	tgc	gtc	tcc	aac	540	
Thr	Arg	His	Met	Glu	Tyr	Thr	Leu	Arg	Thr	Arg	Lys	Cys	Val	Ser	Asn	155	
		145					150				155						
gtc	atg	atc	gcg	ctc	acc	tgg	gca	ctc	tcc	gct	gtc	atc	tct	ctg	gcc	588	
Val	Met	Ile	Ala	Leu	Thr	Trp	Ala	Leu	Ser	Ala	Val	Ile	Ser	Leu	Ala	175	
					165					170							
ccg	ctg	ctt	ttt	ggc	tgg	gga	gag	acg	tac	tct	gag	ggc	agc	gag	gag	636	
Pro	Leu	Leu	Phe	Gly	Trp	Gly	Glu	Thr	Tyr	Ser	Glu	Gly	Ser	Glu	Glu	190	
				180					185								
tgc	cag	gta	agc	cgc	gag	cct	tcc	tac	gcc	gtg	ttc	tcc	acc	gta	ggc	684	
Cys	Gln	Val	Ser	Arg	Glu	Pro	Ser	Tyr	Ala	Val	Phe	Ser	Thr	Val	Gly	205	
			195					200									
gcc	ttc	tac	ctg	ccg	ctc	tgt	gtg	gtg	ctc	ttc	gtg	tac	tgg	aag	atc	732	
Ala	Phe	Tyr	Leu	Pro	Leu	Cys	Val	Val	Leu	Phe	Val	Tyr	Trp	Lys	Ile	220	
		210					215										
tac	aag	gct	gcc	aag	ttc	cgc	gtg	ggc	tcc	agg	aag	acc	aat	agc	gtc	780	
Tyr	Lys	Ala	Ala	Lys	Phe	Arg	Val	Gly	Ser	Arg	Lys	Thr	Asn	Ser	Val	235	
		225					230				235						
tca	ccc	ata	tcc	gaa	gct	gtg	gag	gtg	aag	gac	tct	gcc	aaa	cag	ccc	828	
Ser	Pro	Ile	Ser	Glu	Ala	Val	Glu	Val	Lys	Asp	Ser	Ala	Lys	Gln	Pro	255	
					245					250							
cag	atg	gtg	ttc	acg	gtc	cgc	cac	gcc	acc	gtc	acc	ttc	cag	cca	gaa	876	
Gln	Met	Val	Phe	Thr	Val	Arg	His	Ala	Thr	Val	Thr	Phe	Gln	Pro	Glu	270	
				260					265								
ggg	gac	acg	tgg	cgg	gag	cag	aag	gag	cag	cgg	gcc	gcc	ctc	atg	gtg	924	
Gly	Asp	Thr	Trp	Arg	Glu	Gln	Lys	Glu	Gln	Arg	Ala	Ala	Leu	Met	Val	285	
			275					280									
ggc	atc	ctc	att	ggc	gtg	ttc	gtg	ctc	tgc	tgg	atc	ccc	ttc	ttt	ctc	972	
Gly	Ile	Leu	Ile	Gly	Val	Phe	Val	Leu	Cys	Trp	Ile	Pro	Phe	Phe	Leu	300	
		290					295										
acc	gag	ctc	atc	agt	ccc	ctc	tgc	tcc	tgt	gac	atc	ccc	gcc	atc	tgg	1020	
Thr	Glu	Leu	Ile	Ser	Pro	Leu	Cys	Ser	Cys	Asp	Ile	Pro	Ala	Ile	Trp	315	
		305					310										
aaa	agc	atc	ttc	ctg	tgg	ctt	ggc	tac	tcc	aac	tcc	ttc	ttt	aac	ccc	1068	
Lys	Ser	Ile	Phe	Leu	Trp	Leu	Gly	Tyr	Ser	Asn	Ser	Phe	Phe	Asn	Pro	335	
					325					330							
ctg	atc	tat	acg	gct	ttc	aac	aag	aac	tac	aac	agc	gcc	ttc	aag	aac	1116	
Leu	Ile	Tyr	Thr	Ala	Phe	Asn	Lys	Asn	Tyr	Asn	Ser	Ala	Phe	Lys	Asn		

340

345

350

ttc ttt tct agg caa cac tga gggagaggga ttgatggaat tc
 Phe Phe Ser Arg Gln His *
 355

1159

<210> 38
 <211> 357
 <212> PRT
 <213> Homo Sapiens

<400> 38
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 Pro Leu Glu Thr Asn His Ser Leu Gly Lys Asp Asp Leu Arg Pro Ser
 20 25 30
 Ser Pro Leu Leu Ser Val Phe Gly Val Leu Ile Leu Thr Leu Leu Gly
 35 40 45
 Phe Leu Val Ala Ala Thr Phe Ala Trp Asn Leu Leu Val Leu Ala Thr
 50 55 60
 Ile Leu Arg Val Arg Thr Phe His Arg Val Pro His Asn Leu Val Ala
 65 70 75 80
 Ser Met Ala Val Ser Asp Val Leu Val Ala Ala Leu Val Met Pro Leu
 85 90 95
 Ser Leu Val His Glu Leu Ser Gly Arg Arg Trp Gln Leu Gly Arg Arg
 100 105 110
 Leu Cys Gln Leu Trp Ile Ala Cys Asp Val Leu Cys Cys Thr Ala Ser
 115 120 125
 Ile Trp Asn Val Thr Ala Ile Ala Leu Asp Arg Tyr Trp Ser Ile Thr
 130 135 140
 Arg His Met Glu Tyr Thr Leu Arg Thr Arg Lys Cys Val Ser Asn Val
 145 150 155 160
 Met Ile Ala Leu Thr Trp Ala Leu Ser Ala Val Ile Ser Leu Ala Pro
 165 170 175
 Leu Leu Phe Gly Trp Gly Glu Thr Tyr Ser Glu Gly Ser Glu Glu Cys
 180 185 190
 Gln Val Ser Arg Glu Pro Ser Tyr Ala Val Phe Ser Thr Val Gly Ala
 195 200 205
 Phe Tyr Leu Pro Leu Cys Val Val Leu Phe Val Tyr Trp Lys Ile Tyr
 210 215 220
 Lys Ala Ala Lys Phe Arg Val Gly Ser Arg Lys Thr Asn Ser Val Ser
 225 230 235 240
 Pro Ile Ser Glu Ala Val Glu Val Lys Asp Ser Ala Lys Gln Pro Gln
 245 250 255
 Met Val Phe Thr Val Arg His Ala Thr Val Thr Phe Gln Pro Glu Gly
 260 265 270
 Asp Thr Trp Arg Glu Gln Lys Glu Gln Arg Ala Ala Leu Met Val Gly
 275 280 285
 Ile Leu Ile Gly Val Phe Val Leu Cys Trp Ile Pro Phe Phe Leu Thr
 290 295 300
 Glu Leu Ile Ser Pro Leu Cys Ser Cys Asp Ile Pro Ala Ile Trp Lys
 305 310 315 320
 Ser Ile Phe Leu Trp Leu Gly Tyr Ser Asn Ser Phe Phe Asn Pro Leu
 325 330 335
 Ile Tyr Thr Ala Phe Asn Lys Asn Tyr Asn Ser Ala Phe Lys Asn Phe
 340 345 350
 Phe Ser Arg Gln His
 355

<210> 39
 <211> 1074
 <212> DNA
 <213> Homo Sapiens

<220>
 <221> CDS
 <222> (1)...(1074)

<400> 39
 atg gat tta cca gtg aac cta acc tcc ttt tcc ctc tcc acc ccc tcc 48
 Met Asp Leu Pro Val Asn Leu Thr Ser Phe Ser Leu Ser Thr Pro Ser
 1 5 10 15

cct ttg gag acc aac cac agc ctc ggc aaa gac gac ctg cgc ccc agc 96
 Pro Leu Glu Thr Asn His Ser Leu Gly Lys Asp Asp Leu Arg Pro Ser
 20 25 30

tcg ccc ctg ctc tcg gtc ttc gga gtg ctt att ctc acc ttg ctg ggc 144
 Ser Pro Leu Leu Ser Val Phe Gly Val Leu Ile Leu Thr Leu Leu Gly
 35 40 45

ttt ctg gtg gcg gcg acg ttc gcc tgg aac ctg ctg gtg ctg gcg acc 192
 Phe Leu Val Ala Ala Thr Phe Ala Trp Asn Leu Leu Val Leu Ala Thr
 50 55 60

atc ctc cgt gta cgc acc ttc cac cgc gtg ccc cac aac ctg gtg gca 240
 Ile Leu Arg Val Arg Thr Phe His Arg Val Pro His Asn Leu Val Ala
 65 70 75 80

tcc atg gcc gtc tcg gat gtc ctg gtg gcc gcg ctg gtc atg ccg ctg 288
 Ser Met Ala Val Ser Asp Val Leu Val Ala Ala Leu Val Met Pro Leu
 85 90 95

agc ctg gtg cat gag ctg tcc ggg cgc cgc tgg cag cta ggt cgg agg 336
 Ser Leu Val His Glu Leu Ser Gly Arg Arg Trp Gln Leu Gly Arg Arg
 100 105 110

ctg tgc cag ctt tgg atc gcg tgc gac gtg ctt tgc tgc acg gcc agc 384
 Leu Cys Gln Leu Trp Ile Ala Cys Asp Val Leu Cys Cys Thr Ala Ser
 115 120 125

atc tgg aac gtg acg gcc ata gcc ctg gac cgc tac tgg tcc atc acg 432
 Ile Trp Asn Val Thr Ala Ile Ala Leu Asp Arg Tyr Trp Ser Ile Thr
 130 135 140

cgc cac atg gaa tac acg ctc cgc acc cgc aag tgc gtc tcc aac gtc 480
 Arg His Met Glu Tyr Thr Leu Arg Thr Arg Lys Cys Val Ser Asn Val
 145 150 155 160

atg atc gcg ctc acc tgg gca ctc tcc gct gtc atc tct ctg gcc ccg 528
 Met Ile Ala Leu Thr Trp Ala Leu Ser Ala Val Ile Ser Leu Ala Pro
 165 170 175

ctg ctt ttt ggc tgg gga gag acg tac tct gag ggc agc gag gag tgc 576
 Leu Leu Phe Gly Trp Gly Glu Thr Tyr Ser Glu Gly Ser Glu Glu Cys
 180 185 190

cag gta agc cgc gag cct tcc tac gcc gtg ttc tcc acc gta ggc gcc 624
 Gln Val Ser Arg Glu Pro Ser Tyr Ala Val Phe Ser Thr Val Gly Ala
 195 200 205

ttc tac ctg ccg ctc tgt gtg gtg ctc ttc gtg tac tgg aag atc tac 672
 Phe Tyr Leu Pro Leu Cys Val Val Leu Phe Val Tyr Trp Lys Ile Tyr
 210 215 220

aag gct gcc aag ttc cgc gtg ggc tcc agg aag acc aat agc gtc tca 720
 Lys Ala Ala Lys Phe Arg Val Gly Ser Arg Lys Thr Asn Ser Val Ser
 225 230 235 240

ccc ata tcc gaa gct gtg gag gtg aag gac tct gcc aaa cag ccc cag 768
 Pro Ile Ser Glu Ala Val Glu Val Lys Asp Ser Ala Lys Gln Pro Gln
 245 250 255

atg gtg ttc acg gtc cgc cac gcc acc gtc acc ttc cag cca gaa ggg 816
 Met Val Phe Thr Val Arg His Ala Thr Val Thr Phe Gln Pro Glu Gly
 260 265 270

gac acg tgg cgg gag cag aag gag cag cgg gcc gcc ctc atg gtg ggc 864
 Asp Thr Trp Arg Glu Gln Lys Glu Gln Arg Ala Ala Leu Met Val Gly
 275 280 285
 atc ctc att ggc gtg ttc gtg ctc tgc tgg atc ccc ttc ttt ctc acc 912
 Ile Leu Ile Gly Val Phe Val Leu Cys Trp Ile Pro Phe Phe Leu Thr
 290 295 300
 gag ctc atc agt ccc ctc tgc tcc tgt gac atc ccc gcc atc tgg aaa 960
 Glu Leu Ile Ser Pro Leu Cys Ser Cys Asp Ile Pro Ala Ile Trp Lys
 305 310 315 320
 agc atc ttc ctg tgg ctt ggc tac tcc aac tcc ttc ttt aac ccc ctg 1008
 Ser Ile Phe Leu Trp Leu Gly Tyr Ser Asn Ser Phe Phe Asn Pro Leu
 325 330 335
 atc tat acg gct ttc aac aag aac tac aac agc gcc ttc aag aac ttc 1056
 Ile Tyr Thr Ala Phe Asn Lys Asn Tyr Asn Ser Ala Phe Lys Asn Phe
 340 345 350
 ttt tct agg caa cac tga 1074
 Phe Ser Arg Gln His *
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<210> 40
 <211> 1984
 <212> DNA
 <213> Homo Sapiens

<220>
 <221> CDS
 <222> (468)...(1790)

<400> 40
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 tgaccgggcc ggacgcccct cccctatctt gccgcccgcc ccctccaggg ggctctgtc 120
 ccaccccagg gagcccatcc gacctctgct tgacttcccg ccgcttccct caggggcctc 180
 ggctcatcgg gtgcccctcc ccaaacttcc aaccggtttg ctccaggagt tcctgccccca 240
 tccccgaggg gcgcccata gccacactgt gtctctctgt agtcgccgcc ccctgacctc 300
 gcgcgaccca gcgccccgc ccatgtcccc ccaactcacct ccccggggg gcgtgggtgag 360
 tcgcgggtctg ttctcacgga cgggtccccgt ccagcctgcg cttcgccggg gccctcatct 420
 gctttcccg caccctatca ctcccttgcc gtcacacctc ggtcctc atg gtc cca 476
 Met Val Pro
 1

gag ccg ggc cca acc gcc aat agc acc ccg gcc tgg ggg gca ggg ccg 524
 Glu Pro Gly Pro Thr Ala Asn Ser Thr Pro Ala Trp Gly Ala Gly Pro
 5 10 15

ccg tcg gcc ccg ggg ggc agc ggc tgg gtg gcg gcc gcg ctg tgc gtg 572
 Pro Ser Ala Pro Gly Gly Ser Gly Trp Val Ala Ala Ala Leu Cys Val
 20 25 30 35

gtc atc gcg ctg acg gcg gcg gcc aac tcg ctg ctg atc gcg ctc atc 620
 Val Ile Ala Leu Thr Ala Ala Ala Asn Ser Leu Leu Ile Ala Leu Ile
 40 45 50

tgc act cag ccc gcg ctg cgc aac acg tcc aac ttc ttc ctg gtg tcg 668
 Cys Thr Gln Pro Ala Leu Arg Asn Thr Ser Asn Phe Phe Leu Val Ser
 55 60 65

ctc ttc acg tct gac ctg atg gtg ggg ctg gtg gtg atg ccg ccg gcc 716
 Leu Phe Thr Ser Asp Leu Met Val Gly Leu Val Val Met Pro Pro Ala
 70 75 80

atg ctg aac gcg ctg tac ggg cgc tgg gtg ctg gcg cgc ggc ctc tgc 764
 Met Leu Asn Ala Leu Tyr Gly Arg Trp Val Leu Ala Arg Gly Leu Cys

85	90	95	
ctg ctc tgg acc gcc ttc gac gtg atg tgc tgc agc gcc tcc atc ctc Leu Leu Trp Thr Ala Phe Asp Val Met Cys Cys Ser Ala Ser Ile Leu 100 105 110 115			812
aac ctc tgc ctc atc agc ctg gac cgc tac ctg ctc atc ctc tcg ccg Asn Leu Cys Leu Ile Ser Leu Asp Arg Tyr Leu Leu Ile Leu Ser Pro 120 125 130			860
ctg cgc tac aag ctg cgc atg acg ccc ctg cgt gcc ctg gcc cta gtc Leu Arg Tyr Lys Leu Arg Met Thr Pro Leu Arg Ala Leu Ala Leu Val 135 140 145			908
ctg ggc gcc tgg agc ctc gcc gct ctc gcc tcc ttc ctg ccc ctg ctg Leu Gly Ala Trp Ser Leu Ala Ala Leu Ala Ser Phe Leu Pro Leu Leu 150 155 160			956
ctg ggc tgg cac gag ctg ggc cac gca cgg cca ccc gtc cct ggc cag Leu Gly Trp His Glu Leu Gly His Ala Arg Pro Pro Val Pro Gly Gln 165 170 175			1004
tgc cgc ctg ctg gcc agc ctg cct ttt gtc ctt gtg gcg tcg ggc ctc Cys Arg Leu Leu Ala Ser Leu Pro Phe Val Leu Val Ala Ser Gly Leu 180 185 190 195			1052
acc ttc ttc ctg ccc tcg ggt gcc ata tgc ttc acc tac tgc agg atc Thr Phe Phe Leu Pro Ser Gly Ala Ile Cys Phe Thr Tyr Cys Arg Ile 200 205 210			1100
ctg cta gct gcc cgc aag cag gcc gtg cag gtg gcc tcc ctc acc acc Leu Leu Ala Ala Arg Lys Gln Ala Val Gln Val Ala Ser Leu Thr Thr 215 220 225			1148
ggc atg gcc agt cag gcc tcg gag acg ctg cag gtg ccc agg acc cca Gly Met Ala Ser Gln Ala Ser Glu Thr Leu Gln Val Pro Arg Thr Pro 230 235 240			1196
cgc cca ggg gtg gag tct gct gac agc agg cgt cta gcc acg aag cac Arg Pro Gly Val Glu Ser Ala Asp Ser Arg Arg Leu Ala Thr Lys His 245 250 255			1244
agc agg aag gcc ctg aag gcc agc ctg acg ctg ggc atc ctg ctg ggc Ser Arg Lys Ala Leu Lys Ala Ser Leu Thr Leu Gly Ile Leu Leu Gly 260 265 270 275			1292
atg ttc ttt gtg acc tgg ttg ccc ttc ttt gtg gcc aac ata gtc cag Met Phe Phe Val Thr Trp Leu Pro Phe Phe Val Ala Asn Ile Val Gln 280 285 290			1340
gcc gtg tgc gac tgc atc tcc cca ggc ctc ttc gat gtc ctc aca tgg Ala Val Cys Asp Cys Ile Ser Pro Gly Leu Phe Asp Val Leu Thr Trp 295 300 305			1388
ctg ggt tac tgt aac agc acc atg aac ccc atc atc tac cca ctc ttc Leu Gly Tyr Cys Asn Ser Thr Met Asn Pro Ile Ile Tyr Pro Leu Phe 310 315 320			1436
atg cgg gac ttc aag cgg gcg ctg ggc agg ttc ctg cca tgt cca cgc Met Arg Asp Phe Lys Arg Ala Leu Gly Arg Phe Leu Pro Cys Pro Arg 325 330 335			1484
tgt ccc cgg gag cgc cag gcc agc ctg gcc tcg cca tca ctg cgc acc Cys Pro Arg Glu Arg Gln Ala Ser Leu Ala Ser Pro Ser Leu Arg Thr 340 345 350 355			1532
tct cac agc ggc ccc cgg ccc ggc ctt agc cta cag cag gtg ctg ccg Ser His Ser Gly Pro Arg Pro Gly Leu Ser Leu Gln Gln Val Leu Pro 360 365 370			1580

ctg ccc ctg ccg ccg gac tca gat tcg gac tca gac gca ggc tca ggc 1628
 Leu Pro Leu Pro Pro Asp Ser Asp Ser Asp Ser Asp Ala Gly Ser Gly
 375 380 385
 ggc tcc tcg ggc ctg cgg ctc acg gcc cag ctg ctg ctt cct ggc gag 1676
 Gly Ser Ser Gly Leu Arg Leu Thr Ala Gln Leu Leu Leu Pro Gly Glu
 390 395 400
 gcc acc cag gac ccc ccg ctg ccc acc agg gcc gct gcc gcc gtc aat 1724
 Ala Thr Gln Asp Pro Pro Leu Pro Thr Arg Ala Ala Ala Val Asn
 405 410 415
 ttc ttc aac atc gac ccc gcg gag ccc gag ctg cgg ccg cat cca ctt 1772
 Phe Phe Asn Ile Asp Pro Ala Glu Pro Glu Leu Arg Pro His Pro Leu
 420 425 430 435
 ggc atc ccc acg aac tga cccgggcttg gggctggcca atggggagct 1820
 Gly Ile Pro Thr Asn *
 440

ggattgagca gaacccagac cctgagtctt tgggccagct cttggctaag accaggaggc 1880
 tgcaagtctc ctagaagccc tctgagctcc agaggggtgc gcagagctga cccctgtgtg 1940
 ccatctccag gcccttacc tgcagggatc atagctgact caga 1984

<210> 41
 <211> 440
 <212> PRT
 <213> Homo Sapiens

<400> 41
 Met Val Pro Glu Pro Gly Pro Thr Ala Asn Ser Thr Pro Ala Trp Gly
 1 5 10 15
 Ala Gly Pro Pro Ser Ala Pro Gly Gly Ser Gly Trp Val Ala Ala Ala
 20 25 30
 Leu Cys Val Val Ile Ala Leu Thr Ala Ala Ala Asn Ser Leu Leu Ile
 35 40 45
 Ala Leu Ile Cys Thr Gln Pro Ala Leu Arg Asn Thr Ser Asn Phe Phe
 50 55 60
 Leu Val Ser Leu Phe Thr Ser Asp Leu Met Val Gly Leu Val Val Met
 65 70 75 80
 Pro Pro Ala Met Leu Asn Ala Leu Tyr Gly Arg Trp Val Leu Ala Arg
 85 90 95
 Gly Leu Cys Leu Leu Trp Thr Ala Phe Asp Val Met Cys Cys Ser Ala
 100 105 110
 Ser Ile Leu Asn Leu Cys Leu Ile Ser Leu Asp Arg Tyr Leu Leu Ile
 115 120 125
 Leu Ser Pro Leu Arg Tyr Lys Leu Arg Met Thr Pro Leu Arg Ala Leu
 130 135 140
 Ala Leu Val Leu Gly Ala Trp Ser Leu Ala Ala Leu Ala Ser Phe Leu
 145 150 155 160
 Pro Leu Leu Leu Gly Trp His Glu Leu Gly His Ala Arg Pro Pro Val
 165 170 175
 Pro Gly Gln Cys Arg Leu Leu Ala Ser Leu Pro Phe Val Leu Val Ala
 180 185 190
 Ser Gly Leu Thr Phe Phe Leu Pro Ser Gly Ala Ile Cys Phe Thr Tyr
 195 200 205
 Cys Arg Ile Leu Leu Ala Ala Arg Lys Gln Ala Val Gln Val Ala Ser
 210 215 220
 Leu Thr Thr Gly Met Ala Ser Gln Ala Ser Glu Thr Leu Gln Val Pro
 225 230 235 240
 Arg Thr Pro Arg Pro Gly Val Glu Ser Ala Asp Ser Arg Arg Leu Ala
 245 250 255
 Thr Lys His Ser Arg Lys Ala Leu Lys Ala Ser Leu Thr Leu Gly Ile
 260 265 270
 Leu Leu Gly Met Phe Phe Val Thr Trp Leu Pro Phe Phe Val Ala Asn
 275 280 285
 Ile Val Gln Ala Val Cys Asp Cys Ile Ser Pro Gly Leu Phe Asp Val
 290 295 300

Leu Thr Trp Leu Gly Tyr Cys Asn Ser Thr Met Asn Pro Ile Ile Tyr
 305 310 315 320
 Pro Leu Phe Met Arg Asp Phe Lys Arg Ala Leu Gly Arg Phe Leu Pro
 325 330 335
 Cys Pro Arg Cys Pro Arg Glu Arg Gln Ala Ser Leu Ala Ser Pro Ser
 340 345 350
 Leu Arg Thr Ser His Ser Gly Pro Arg Pro Gly Leu Ser Leu Gln Gln
 355 360 365
 Val Leu Pro Leu Pro Leu Pro Asp Ser Asp Ser Asp Ser Asp Ala
 370 375 380
 Gly Ser Gly Gly Ser Ser Gly Leu Arg Leu Thr Ala Gln Leu Leu Leu
 385 390 395 400
 Pro Gly Glu Ala Thr Gln Asp Pro Pro Leu Pro Thr Arg Ala Ala Ala
 405 410 415
 Ala Val Asn Phe Phe Asn Ile Asp Pro Ala Glu Pro Glu Leu Arg Pro
 420 425 430
 His Pro Leu Gly Ile Pro Thr Asn
 435 440

<210> 42

<211> 1323

<212> DNA

<213> Homo Sapiens

<220>

<221> CDS

<222> (1)...(1323)

<400> 42

atg gtc cca gag ccg ggc cca acc gcc aat agc acc ccg gcc tgg ggg	48
Met Val Pro Glu Pro Gly Pro Thr Ala Asn Ser Thr Pro Ala Trp Gly	
1 5 10 15	
gca ggg ccg ccg tcg gcc ccg ggg ggc agc ggc tgg gtg gcg gcc gcg	96
Ala Gly Pro Pro Ser Ala Pro Gly Gly Ser Gly Trp Val Ala Ala Ala	
20 25 30	
ctg tgc gtg gtc atc gcg ctg acg gcg gcg gcc aac tcg ctg ctg atc	144
Leu Cys Val Val Ile Ala Leu Thr Ala Ala Ala Asn Ser Leu Leu Ile	
35 40 45	
gcg ctc atc tgc act cag ccc gcg ctg cgc aac acg tcc aac ttc ttc	192
Ala Leu Ile Cys Thr Gln Pro Ala Leu Arg Asn Thr Ser Asn Phe Phe	
50 55 60	
ctg gtg tcg ctc ttc acg tct gac ctg atg gtg ggg ctg gtg gtg atg	240
Leu Val Ser Leu Phe Thr Ser Asp Leu Met Val Gly Leu Val Val Met	
65 70 75 80	
ccg ccg gcc atg ctg aac gcg ctg tac ggg cgc tgg gtg ctg gcg gcg	288
Pro Pro Ala Met Leu Asn Ala Leu Tyr Gly Arg Trp Val Leu Ala Arg	
85 90 95	
ggc ctc tgc ctg ctc tgg acc gcc ttc gac gtg atg tgc tgc agc gcc	336
Gly Leu Cys Leu Leu Trp Thr Ala Phe Asp Val Met Cys Cys Ser Ala	
100 105 110	
tcc atc ctc aac ctc tgc ctc atc agc ctg gac cgc tac ctg ctc atc	384
Ser Ile Leu Asn Leu Cys Leu Ile Ser Leu Asp Arg Tyr Leu Leu Ile	
115 120 125	
ctc tcg ccg ctg cgc tac aag ctg cgc atg acg ccc ctg cgt gcc ctg	432
Leu Ser Pro Leu Arg Tyr Lys Leu Arg Met Thr Pro Leu Arg Ala Leu	
130 135 140	
gcc cta gtc ctg ggc gcc tgg agc ctc gcc gct ctc gcc tcc ttc ctg	480
Ala Leu Val Leu Gly Ala Trp Ser Leu Ala Leu Ala Ser Phe Leu	
145 150 155 160	

ccc ctg ctg ctg ggc tgg cac gag ctg ggc cac gca cgg cca ccc gtc	528
Pro Leu Leu Leu Gly Trp His Glu Leu Gly His Ala Arg Pro Pro Val	
165 170 175	
cct ggc cag tgc cgc ctg ctg gcc agc ctg cct ttt gtc ctt gtg gcg	576
Pro Gly Gln Cys Arg Leu Leu Ala Ser Leu Pro Phe Val Leu Val Ala	
180 185 190	
tcg ggc ctc acc ttc ttc ctg ccc tcg ggt gcc ata tgc ttc acc tac	624
Ser Gly Leu Thr Phe Phe Leu Pro Ser Gly Ala Ile Cys Phe Thr Tyr	
195 200 205	
tgc agg atc ctg cta gct gcc cgc aag cag gcc gtg cag gtg gcc tcc	672
Cys Arg Ile Leu Leu Ala Ala Arg Lys Gln Ala Val Gln Val Ala Ser	
210 215 220	
ctc acc acc ggc atg gcc agt cag gcc tcg gag acg ctg cag gtg ccc	720
Leu Thr Thr Gly Met Ala Ser Gln Ala Ser Glu Thr Leu Gln Val Pro	
225 230 235 240	
agg acc cca cgc cca ggg gtg gag tct gct gac agc agg cgt cta gcc	768
Arg Thr Pro Arg Pro Gly Val Glu Ser Ala Asp Ser Arg Arg Leu Ala	
245 250 255	
acg aag cac agc agg aag gcc ctg aag gcc agc ctg acg ctg ggc atc	816
Thr Lys His Ser Arg Lys Ala Leu Lys Ala Ser Leu Thr Leu Gly Ile	
260 265 270	
ctg ctg ggc atg ttc ttt gtg acc tgg ttg ccc ttc ttt gtg gcc aac	864
Leu Leu Gly Met Phe Phe Val Thr Trp Leu Pro Phe Phe Val Ala Asn	
275 280 285	
ata gtc cag gcc gtg tgc gac tgc atc tcc cca ggc ctc ttc gat gtc	912
Ile Val Gln Ala Val Cys Asp Cys Ile Ser Pro Gly Leu Phe Asp Val	
290 295 300	
ctc aca tgg ctg ggt tac tgt aac agc acc atg aac ccc atc atc tac	960
Leu Thr Trp Leu Gly Tyr Cys Asn Ser Thr Met Asn Pro Ile Ile Tyr	
305 310 315 320	
cca ctc ttc atg cgg gac ttc aag cgg gcg ctg ggc agg ttc ctg cca	1008
Pro Leu Phe Met Arg Asp Phe Lys Arg Ala Leu Gly Arg Phe Leu Pro	
325 330 335	
tgt cca cgc tgt ccc cgg gag cgc cag gcc agc ctg gcc tcg cca tca	1056
Cys Pro Arg Cys Pro Arg Glu Arg Gln Ala Ser Leu Ala Ser Pro Ser	
340 345 350	
ctg cgc acc tct cac agc ggc ccc cgg ccc ggc ctt agc cta cag cag	1104
Leu Arg Thr Ser His Ser Gly Pro Arg Pro Gly Leu Ser Leu Gln Gln	
355 360 365	
gtg ctg ccg ctg ccc ctg ccg ccg gac tca gat tcg gac tca gac gca	1152
Val Leu Pro Leu Pro Leu Pro Pro Asp Ser Asp Ser Asp Ser Ala	
370 375 380	
ggc tca ggc ggc tcc tcg ggc ctg cgg ctc acg gcc cag ctg ctg ctt	1200
Gly Ser Gly Gly Ser Ser Gly Leu Arg Leu Thr Ala Gln Leu Leu Leu	
385 390 395 400	
cct ggc gag gcc acc cag gac ccc ccg ctg ccc acc agg gcc gct gcc	1248
Pro Gly Glu Ala Thr Gln Asp Pro Pro Leu Pro Thr Arg Ala Ala Ala	
405 410 415	
gcc gtc aat ttc ttc aac atc gac ccc gcg gag ccc gag ctg cgg ccg	1296
Ala Val Asn Phe Phe Asn Ile Asp Pro Ala Glu Pro Glu Leu Arg Pro	
420 425 430	

cat cca ctt ggc atc ccc acg aac tga
 His Pro Leu Gly Ile Pro Thr Asn *
 435 440

1323

<210> 43
 <211> 2772
 <212> DNA
 <213> Homo Sapiens

<220>
 <221> CDS
 <222> (64)...(1323)

<400> 43
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 gac atg acg aca gct ccc cag gag ccc ccc gcc cgg ccc ctc cag gcg 108
 Met Thr Thr Ala Pro Gln Glu Pro Pro Ala Arg Pro Leu Gln Ala 15
 1 5 10 15

 ggc agt gga gct ggc ccg gcg cct ggg cgc gcc atg cgc agc acc acg 156
 Gly Ser Gly Ala Gly Pro Ala Pro Gly Arg Ala Met Arg Ser Thr Thr 30
 20 25 30

 ctc ctg gcc ctg ctg gcg ctg gtc ttg ctt tac ttg gtg tct ggt gcc 204
 Leu Leu Ala Leu Leu Ala Leu Val Leu Leu Tyr Leu Val Ser Gly Ala 45
 35 40 45

 ctg gtg ttc cgg gcc ctg gag cag ccc cac gag cag cag gcc cag agg 252
 Leu Val Phe Arg Ala Leu Glu Gln Pro His Glu Gln Gln Ala Gln Arg 60
 50 55 60

 gag ctg ggg gag gtc cga gag aag ttc ctg agg gcc cat ccg tgt gtg 300
 Glu Leu Gly Glu Val Arg Glu Lys Phe Leu Arg Ala His Pro Cys Val 75
 65 70 75

 agc gac cag gag ctg ggc ctc ctc atc aag gag gtg gct gat gcc ctg 348
 Ser Asp Gln Glu Leu Gly Leu Leu Ile Lys Glu Val Ala Asp Ala Leu 95
 80 85 90 95

 gga ggg ggt gcg gac cca gaa acc aac tcg acc agc aac agc agc cac 396
 Gly Gly Gly Ala Asp Pro Glu Thr Asn Ser Thr Ser Asn Ser Ser His 110
 100 105 110

 tca gcc tgg gac ctg ggc agc gcc ttc ttt ttc tca ggg acc atc atc 444
 Ser Ala Trp Asp Leu Gly Ser Ala Phe Phe Phe Ser Gly Thr Ile Ile 125
 115 120 125

 acc acc atc ggc tat ggc aat gtg gcc ctg cgc aca gat gcc ggg cgc 492
 Thr Thr Ile Gly Tyr Gly Asn Val Ala Leu Arg Thr Asp Ala Gly Arg 140
 130 135 140

 ctc ttc tgc atc ttc tat gcg ctg gtg ggg att ccg ctg ttt ggg atc 540
 Leu Phe Cys Ile Phe Tyr Ala Leu Val Gly Ile Pro Leu Phe Gly Ile 155
 145 150 155

 cta ctg gca ggg gtc ggg gac cgg ctg ggc tcc tcc ctg cgc cat gcc 588
 Leu Leu Ala Gly Val Gly Asp Arg Leu Gly Ser Ser Leu Arg His Gly 175
 160 165 170 175

 atc ggt cac att gaa gcc atc ttc ttg aag tgg cac gtg cca ccg gag 636
 Ile Gly His Ile Glu Ala Ile Phe Leu Lys Trp His Val Pro Pro Glu 190
 180 185 190

 cta gta aga gtg ctg tcg gcg atg ctt ttc ctg ctg atc ggc tgc ctg 684
 Leu Val Arg Val Leu Ser Ala Met Leu Phe Leu Leu Ile Gly Cys Leu 205
 195 200 205

 ctc ttt gtc ctc acg ccc acg ttc gtg ttc tgc tat atg gag gac tgg 732

Leu	Phe	Val	Leu	Thr	Pro	Thr	Phe	Val	Phe	Cys	Tyr	Met	Glu	Asp	Trp	
		210					215					220				
agc	aag	ctg	gag	gcc	atc	tac	ttt	gtc	ata	gtg	acg	ctt	acc	acc	gtg	780
Ser	Lys	Leu	Glu	Ala	Ile	Tyr	Phe	Val	Ile	Val	Thr	Leu	Thr	Thr	Val	
	225				230						235					
ggc	ttt	ggc	gac	tat	gtg	gcc	ggc	gcg	gac	ccc	agg	cag	gac	tcc	ccg	828
Gly	Phe	Gly	Asp	Tyr	Val	Ala	Gly	Ala	Asp	Pro	Arg	Gln	Asp	Ser	Pro	
240					245					250					255	
gcc	tat	cag	ccg	ctg	gtg	tgg	ttc	tgg	atc	ctg	ctc	ggc	ctg	gct	tac	876
Ala	Tyr	Gln	Pro	Leu	Val	Trp	Phe	Trp	Ile	Leu	Leu	Gly	Leu	Ala	Tyr	
				260					265						270	
ttc	gcc	tca	gtg	ctc	acc	acc	atc	ggg	aac	tgg	ctg	cga	gta	gtg	tcc	924
Phe	Ala	Ser	Val	Leu	Thr	Thr	Ile	Gly	Asn	Trp	Leu	Arg	Val	Val	Ser	
			275					280							285	
cgc	cgc	act	cgg	gca	gag	atg	ggc	ggc	ctc	acg	gct	cag	gct	gcc	agc	972
Arg	Arg	Thr	Arg	Ala	Glu	Met	Gly	Gly	Leu	Thr	Ala	Gln	Ala	Ala	Ser	
		290					295						300			
tgg	act	ggc	aca	gtg	aca	gcg	cgc	gtg	acc	cag	cga	gcc	ggg	ccc	gcc	1020
Trp	Thr	Gly	Thr	Val	Thr	Ala	Arg	Val	Thr	Gln	Arg	Ala	Gly	Pro	Ala	
	305					310					315					
gcc	ccg	ccg	ccg	gag	aag	gag	cag	cca	ctg	ctg	cct	cca	ccg	ccc	tgt	1068
Ala	Pro	Pro	Pro	Glu	Lys	Glu	Gln	Pro	Leu	Leu	Pro	Pro	Pro	Pro	Cys	
320					325					330					335	
cca	gcg	cag	ccg	ctg	ggc	agg	ccc	cga	tcc	cct	tcg	ccc	ccc	gag	aag	1116
Pro	Ala	Gln	Pro	Leu	Gly	Arg	Pro	Arg	Ser	Pro	Ser	Pro	Pro	Glu	Lys	
				340					345						350	
gct	cag	ctg	cct	tcc	ccg	ccc	acg	gcc	tcg	gcc	ctg	gat	tat	ccc	agc	1164
Ala	Gln	Leu	Pro	Ser	Pro	Pro	Thr	Ala	Ser	Ala	Leu	Asp	Tyr	Pro	Ser	
			355					360							365	
gag	aac	ctg	gcc	ttc	atc	gac	gag	tcc	tcg	gat	acg	cag	agc	gag	cgc	1212
Glu	Asn	Leu	Ala	Phe	Ile	Asp	Glu	Ser	Ser	Asp	Thr	Gln	Ser	Glu	Arg	
		370					375								380	
ggc	tgc	ccg	ctg	ccc	cgc	gcg	ccg	aga	ggt	cgc	cgc	cgc	cca	aat	ccc	1260
Gly	Cys	Pro	Leu	Pro	Arg	Ala	Pro	Arg	Gly	Arg	Arg	Arg	Pro	Asn	Pro	
	385					390									395	
ccc	agg	aag	ccc	gtg	cgg	ccc	cgc	ggc	ccc	ggg	cgt	ccc	cga	gac	aaa	1308
Pro	Arg	Lys	Pro	Val	Arg	Pro	Arg	Gly	Pro	Gly	Arg	Pro	Arg	Asp	Lys	
400					405					410					415	
ggc	gtg	ccg	gtg	tag	gggcaggatc	cctggccggg	cctctcaagg	gcttcgtttc								1363
Gly	Val	Pro	Val	*												

tgctctcccc	ggcatgcctg	gcttggttga	ccaaagagcc	ctctttccac	gagactgaag	1423
tctgggggagg	aggctacagt	tgctctccg	cctcctccct	ggccccggcc	cttccctcac	1483
ttccatccat	ctctagaccc	ccccaggct	ttctgtgtcg	ctgccccggg	cgggtgtatc	1543
cctcacagca	cctcacgact	gtgcctcaaa	gcctgcatca	ataaatgaaa	acggtctgca	1603
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ctcgtctcga	ggcctgtggc	gtctgggtcc	gttggggcag	aaccatggag	gaaaagcctt	2023
cgaagtgtc	gctcaagtct	tccgaccgcc	aaggctcgga	cgaggagagc	gtgcatagcg	2083
acactcggga	cctgtggacc	acgaccacgc	tgtcccaggc	acagctgaac	atgccgctgt	2143
ccgaggtctg	cgagggtctc	gacgaggagg	gccgcaacat	tagcaagacc	cgcgggtggc	2203

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acagcccggg gcggggctcg ttggacgagg ggtacaaggc cagccacaag ccggaggaac 2263
tggaacgagca cgcgctgggtg gagctggagt tgcaccgagg cagctccatg gaaatcaatc 2323
tggggggagaa ggacactgca tcccagatcg aggccgaaaa gtcttcctca atgtcatcac 2383
tcaatattgc gaagcacatg ccccatcgag cctactgggc agagcagcag agcaggctgc 2443
cactgccccct gatggaactc atggagaatg aagctctgga aatcctcacc aaagccctcc 2503
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tcgaagggct caagaagcgc cggagcaaga ggctgtacgt gaattaaaaa cgccaccttg 2623
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<210> 44

<211> 419

<212> PRT

<213> Homo Sapiens

<400> 44

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35     40     45
Val Phe Arg Ala Leu Glu Gln Pro His Glu Gln Gln Ala Gln Arg Glu
50     55     60
Leu Gly Glu Val Arg Glu Lys Phe Leu Arg Ala His Pro Cys Val Ser
65     70     75     80
Asp Gln Glu Leu Gly Leu Leu Ile Lys Glu Val Ala Asp Ala Leu Gly
85     90     95
Gly Gly Ala Asp Pro Glu Thr Asn Ser Thr Ser Asn Ser Ser His Ser
100    105    110
Ala Trp Asp Leu Gly Ser Ala Phe Phe Ser Gly Thr Ile Ile Thr
115    120    125
Thr Ile Gly Tyr Gly Asn Val Ala Leu Arg Thr Asp Ala Gly Arg Leu
130    135    140
Phe Cys Ile Phe Tyr Ala Leu Val Gly Ile Pro Leu Phe Gly Ile Leu
145    150    155    160
Leu Ala Gly Val Gly Asp Arg Leu Gly Ser Ser Leu Arg His Gly Ile
165    170    175
Gly His Ile Glu Ala Ile Phe Leu Lys Trp His Val Pro Pro Glu Leu
180    185    190
Val Arg Val Leu Ser Ala Met Leu Phe Leu Leu Ile Gly Cys Leu Leu
195    200    205
Phe Val Leu Thr Pro Thr Phe Val Phe Cys Tyr Met Glu Asp Trp Ser
210    215    220
Lys Leu Glu Ala Ile Tyr Phe Val Ile Val Thr Leu Thr Thr Val Gly
225    230    235    240
Phe Gly Asp Tyr Val Ala Gly Ala Asp Pro Arg Gln Asp Ser Pro Ala
245    250    255
Tyr Gln Pro Leu Val Trp Phe Trp Ile Leu Leu Gly Leu Ala Tyr Phe
260    265    270
Ala Ser Val Leu Thr Thr Ile Gly Asn Trp Leu Arg Val Val Ser Arg
275    280    285
Arg Thr Arg Ala Glu Met Gly Gly Leu Thr Ala Gln Ala Ala Ser Trp
290    295    300
Thr Gly Thr Val Thr Ala Arg Val Thr Gln Arg Ala Gly Pro Ala Ala
305    310    315    320
Pro Pro Pro Glu Lys Glu Gln Pro Leu Leu Pro Pro Pro Pro Cys Pro
325    330    335
Ala Gln Pro Leu Gly Arg Pro Arg Ser Pro Ser Pro Pro Glu Lys Ala
340    345    350
Gln Leu Pro Ser Pro Pro Thr Ala Ser Ala Leu Asp Tyr Pro Ser Glu
355    360    365
Asn Leu Ala Phe Ile Asp Glu Ser Ser Asp Thr Gln Ser Glu Arg Gly
370    375    380
Cys Pro Leu Pro Arg Ala Pro Arg Gly Arg Arg Pro Asn Pro Pro
385    390    395    400
Arg Lys Pro Val Arg Pro Arg Gly Pro Gly Arg Pro Arg Asp Lys Gly
405    410    415

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Val Pro Val

<210> 45
 <211> 1260
 <212> DNA
 <213> Homo Sapiens

<220>
 <221> CDS
 <222> (1)...(1260)

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agt gga gct ggc ccg gcg cct ggg cgc gcc atg cgc agc acc acg ctc 96
 Ser Gly Ala Gly Pro Ala Pro Gly Arg Ala Met Arg Ser Thr Thr Leu
 20 25 30

ctg gcc ctg ctg gcg ctg gtc ttg ctt tac ttg gtg tct ggt gcc ctg 144
 Leu Ala Leu Leu Ala Leu Val Leu Leu Tyr Leu Val Ser Gly Ala Leu
 35 40 45

gtg ttc cgg gcc ctg gag cag ccc cac gag cag cag gcc cag agg gag 192
 Val Phe Arg Ala Leu Glu Gln Pro His Glu Gln Gln Ala Gln Arg Glu
 50 55 60

ctg ggg gag gtc cga gag aag ttc ctg agg gcc cat ccg tgt gtg agc 240
 Leu Gly Glu Val Arg Glu Lys Phe Leu Arg Ala His Pro Cys Val Ser
 65 70 75 80

gac cag gag ctg ggc ctc ctc atc aag gag gtg gct gat gcc ctg gga 288
 Asp Gln Glu Leu Gly Leu Leu Ile Lys Glu Val Ala Asp Ala Leu Gly
 85 90 95

ggg ggt gcg gac cca gaa acc aac tcg acc agc aac agc agc cac tca 336
 Gly Gly Ala Asp Pro Glu Thr Asn Ser Thr Ser Asn Ser Ser His Ser
 100 105 110

gcc tgg gac ctg ggc agc gcc ttc ttt ttc tca ggg acc atc atc acc 384
 Ala Trp Asp Leu Gly Ser Ala Phe Phe Ser Gly Thr Ile Ile Thr
 115 120 125

acc atc ggc tat ggc aat gtg gcc ctg cgc aca gat gcc ggg cgc ctc 432
 Thr Ile Gly Tyr Gly Asn Val Ala Leu Arg Thr Asp Ala Gly Arg Leu
 130 135 140

ttc tgc atc ttc tat gcg ctg gtg ggg att ccg ctg ttt ggg atc cta 480
 Phe Cys Ile Phe Tyr Ala Leu Val Gly Ile Pro Leu Phe Gly Ile Leu
 145 150 155 160

ctg gca ggg gtc ggg gac cgg ctg ggc tcc tcc ctg cgc cat ggc atc 528
 Leu Ala Gly Val Gly Asp Arg Leu Gly Ser Ser Leu Arg His Gly Ile
 165 170 175

ggt cac att gaa gcc atc ttc ttg aag tgg cac gtg cca ccg gag cta 576
 Gly His Ile Glu Ala Ile Phe Leu Lys Trp His Val Pro Pro Glu Leu
 180 185 190

gta aga gtg ctg tcg gcg atg ctt ttc ctg ctg atc ggc tgc ctg ctc 624
 Val Arg Val Leu Ser Ala Met Leu Phe Leu Leu Ile Gly Cys Leu Leu
 195 200 205

ttt gtc ctc acg ccc acg ttc gtg ttc tgc tat atg gag gac tgg agc 672
 Phe Val Leu Thr Pro Thr Phe Val Phe Cys Tyr Met Glu Asp Trp Ser
 210 215 220

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aag ctg gag gcc atc tac ttt gtc ata gtg acg ctt acc acc gtg ggc 720
Lys Leu Glu Ala Ile Tyr Phe Val Ile Val Thr Leu Thr Thr Val Gly
225 230 235 240

ttt ggc gac tat gtg gcc gcc gcg gac ccc agg cag gac tcc ccg gcc 768
Phe Gly Asp Tyr Val Ala Gly Ala Asp Pro Arg Gln Asp Ser Pro Ala
245 250 255

tat cag ccg ctg gtg tgg ttc tgg atc ctg ctc ggc ctg gct tac ttc 816
Tyr Gln Pro Leu Val Trp Phe Trp Ile Leu Leu Gly Leu Ala Tyr Phe
260 265 270

gcc tca gtg ctc acc acc atc ggg aac tgg ctg cga gta gtg tcc cgc 864
Ala Ser Val Leu Thr Thr Ile Gly Asn Trp Leu Arg Val Val Ser Arg
275 280 285

cgc act cgg gca gag atg gcc gcc ctc acg gct cag gct gcc agc tgg 912
Arg Thr Arg Ala Glu Met Gly Gly Leu Thr Ala Gln Ala Ala Ser Trp
290 295 300

act ggc aca gtg aca gcg cgc gtg acc cag cga gcc ggg ccc gcc gcc 960
Thr Gly Thr Val Thr Ala Arg Val Thr Gln Arg Ala Gly Pro Ala Ala
305 310 315 320

ccg ccg ccg gag aag gag cag cca ctg ctg cct cca ccg ccc tgt cca 1008
Pro Pro Pro Glu Lys Glu Gln Pro Leu Leu Pro Pro Pro Pro Cys Pro
325 330 335

gcg cag ccg ctg gcc agg ccc cga tcc cct tcg ccc ccc gag aag gct 1056
Ala Gln Pro Leu Gly Arg Pro Arg Ser Pro Ser Pro Pro Glu Lys Ala
340 345 350

cag ctg cct tcc ccg ccc acg gcc tcg gcc ctg gat tat ccc agc gag 1104
Gln Leu Pro Ser Pro Pro Thr Ala Ser Ala Leu Asp Tyr Pro Ser Glu
355 360 365

aac ctg gcc ttc atc gac gag tcc tcg gat acg cag agc gag cgc gcc 1152
Asn Leu Ala Phe Ile Asp Glu Ser Ser Asp Thr Gln Ser Glu Arg Gly
370 375 380

tgc ccg ctg ccc cgc gcg ccg aga ggt cgc cgc cgc cca aat ccc ccc 1200
Cys Pro Leu Pro Arg Ala Pro Arg Gly Arg Arg Arg Pro Asn Pro Pro
385 390 395 400

agg aag ccc gtg cgg ccc cgc gcc ccc ggg cgt ccc cga gac aaa gcc 1248
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gtg ccg gtg tag 1260
Val Pro Val *
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<210> 46
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<220>
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<222> (88)...(2004)
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Met Lys Gly Gly Cys Val Ser Gln Trp
1 5
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aag gcg gcc gcc ggg ttc ctc ttc tgt gtc atg gtt ttt gca tct gct	162
Lys Ala Ala Ala Gly Phe Leu Phe Cys Val Met Val Phe Ala Ser Ala	
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gag cga ccg gtc ttc acg aat cat ttt ctt gtg gag ttg cat aaa ggg	210
Glu Arg Pro Val Phe Thr Asn His Phe Leu Val Glu Leu His Lys Gly	
30 35 40	
gga gag gac aaa gct cgc caa gtt gca gca gaa cac ggc ttt gga gtc	258
Gly Glu Asp Lys Ala Arg Gln Val Ala Ala Glu His Gly Phe Gly Val	
45 50 55	
cga aag ctt ccc ttt gct gaa ggt ctg tac cac ttt tat cac aat ggc	306
Arg Lys Leu Pro Phe Ala Glu Gly Leu Tyr His Phe Tyr His Asn Gly	
60 65 70	
ctt gca aag gcc aag aga aga cgc agc cta cac cac aag cag cag ctg	354
Leu Ala Lys Ala Lys Arg Arg Arg Ser Leu His His Lys Gln Gln Leu	
75 80 85	
gag aga gac ccc agg gta aag atg gct ttg cag cag gaa gga ttt gac	402
Glu Arg Asp Pro Arg Val Lys Met Ala Leu Gln Gln Glu Gly Phe Asp	
90 95 100 105	
cga aaa aag cga ggt tac aga gac atc aat gag atc gac atc aac atg	450
Arg Lys Lys Arg Gly Tyr Arg Asp Ile Asn Glu Ile Asp Ile Asn Met	
110 115 120	
aac gat cct ctt ttt aca aag cag tgg tat ctg atc aat act ggg caa	498
Asn Asp Pro Leu Phe Thr Lys Gln Trp Tyr Leu Ile Asn Thr Gly Gln	
125 130 135	
gct gat ggc act cct ggc ctt gat ttg aat gtg gct gaa gcc tgg gag	546
Ala Asp Gly Thr Pro Gly Leu Asp Leu Asn Val Ala Glu Ala Trp Glu	
140 145 150	
ctg gga tac aca ggg aaa ggt gtt acc att gga att atg gat gat ggg	594
Leu Gly Tyr Thr Gly Lys Gly Val Thr Ile Gly Ile Met Asp Asp Gly	
155 160 165	
att gac tat ctc cac ccg gac ctg gcc tcc aac tat aat gcc gaa gca	642
Ile Asp Tyr Leu His Pro Asp Leu Ala Ser Asn Tyr Asn Ala Glu Ala	
170 175 180 185	
agt tac gac ttc agc agc aac gac ccc tat cct tac cct cgg tac aca	690
Ser Tyr Asp Phe Ser Ser Asn Asp Pro Tyr Pro Tyr Pro Arg Tyr Thr	
190 195 200	
gat gac tgg ttt aac agc cac ggg acc cga tgt gca gga gaa gtt tct	738
Asp Asp Trp Phe Asn Ser His Gly Thr Arg Cys Ala Gly Glu Val Ser	
205 210 215	
gct gcc gcc aac aac aat atc tgt gga gtt gga gta gca tac aac tcc	786
Ala Ala Ala Asn Asn Asn Ile Cys Gly Val Gly Val Ala Tyr Asn Ser	
220 225 230	
aag gtt gca ggc atc cgg atg ctg gac cag cca ttc atg aca gac atc	834
Lys Val Ala Gly Ile Arg Met Leu Asp Gln Pro Phe Met Thr Asp Ile	
235 240 245	
atc gag gcc tcc tcc atc agt cat atg cca cag ctg att gac atc tac	882
Ile Glu Ala Ser Ser Ile Ser His Met Pro Gln Leu Ile Asp Ile Tyr	
250 255 260 265	
agc gcc agc tgg ggc ccc aca gac aac ggc aag aca gtg gat ggg ccc	930
Ser Ala Ser Trp Gly Pro Thr Asp Asn Gly Lys Thr Val Asp Gly Pro	
270 275 280	
cgg gac gtc acg ctg cag gcc atg gcc gat ggc gtg aac aag ggc cgc	978

Arg	Asp	Val	Thr	Leu	Gln	Ala	Met	Ala	Asp	Gly	Val	Asn	Lys	Gly	Arg	
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ggc	ggc	aaa	ggc	agc	atc	tac	gtg	tgg	gcc	tcc	ggg	gac	ggc	ggc	agc	1026
Gly	Gly	Lys	Gly	Ser	Ile	Tyr	Val	Trp	Ala	Ser	Gly	Asp	Gly	Gly	Ser	
		300					305					310				
tat	gac	gac	tgc	aac	tgc	gac	ggc	tac	gcc	tcc	agc	atg	tgg	acc	atc	1074
Tyr	Asp	Asp	Cys	Asn	Cys	Asp	Gly	Tyr	Ala	Ser	Ser	Met	Trp	Thr	Ile	
	315					320					325					
tcc	atc	aac	tca	gcc	atc	aac	gac	ggc	agg	act	gcc	ctg	tac	gac	gag	1122
Ser	Ile	Asn	Ser	Ala	Ile	Asn	Asp	Gly	Arg	Thr	Ala	Leu	Tyr	Asp	Glu	
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agc	tgc	tct	tcc	acc	ttg	gct	tcc	acc	ttc	agc	aac	ggg	agg	aaa	agg	1170
Ser	Cys	Ser	Ser	Thr	Leu	Ala	Ser	Thr	Phe	Ser	Asn	Gly	Arg	Lys	Arg	
				350					355					360		
aac	ccc	gag	gcc	ggt	gtg	gca	acc	aca	gat	ttg	tac	ggc	aac	tgc	act	1218
Asn	Pro	Glu	Ala	Gly	Val	Ala	Thr	Thr	Asp	Leu	Tyr	Gly	Asn	Cys	Thr	
			365					370					375			
ctg	agg	cat	tct	ggg	aca	tct	gca	gct	gcc	ccc	gag	gca	gct	ggt	gtg	1266
Leu	Arg	His	Ser	Gly	Thr	Ser	Ala	Ala	Ala	Pro	Glu	Ala	Ala	Gly	Val	
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Phe	Ala	Leu	Ala	Leu	Glu	Ala	Asn	Leu	Gly	Leu	Thr	Trp	Arg	Asp	Met	
	395					400					405					
cag	cat	ctg	act	gtg	ctc	acc	tcc	aaa	cgg	aac	cag	ctt	cac	gac	gag	1362
Gln	His	Leu	Thr	Val	Leu	Thr	Ser	Lys	Arg	Asn	Gln	Leu	His	Asp	Glu	
410					415					420					425	
gtc	cat	cag	tgg	cgg	cgc	aat	ggg	gtc	ggc	ctg	gaa	ttt	aat	cac	ctc	1410
Val	His	Gln	Trp	Arg	Arg	Asn	Gly	Val	Gly	Leu	Glu	Phe	Asn	His	Leu	
				430					435					440		
ttt	ggc	tac	ggg	gtc	ctt	gat	gca	ggt	gcc	atg	gtg	aaa	atg	gct	aaa	1458
Phe	Gly	Tyr	Gly	Val	Leu	Asp	Ala	Gly	Ala	Met	Val	Lys	Met	Ala	Lys	
			445					450					455			
gac	tgg	aaa	acc	gtg	cct	gag	aga	ttc	cac	tgt	gtg	gga	ggc	tcc	gtg	1506
Asp	Trp	Lys	Thr	Val	Pro	Glu	Arg	Phe	His	Cys	Val	Gly	Gly	Ser	Val	
		460					465					470				
cag	gac	cct	gag	aaa	ata	cca	tcc	act	ggc	aag	ttg	gtg	ctg	aca	ctc	1554
Gln	Asp	Pro	Glu	Lys	Ile	Pro	Ser	Thr	Gly	Lys	Leu	Val	Leu	Thr	Leu	
	475					480					485					
aca	acc	gac	gcc	tgt	gag	ggg	aag	gaa	aat	ttt	gtc	cgc	tac	ctg	gag	1602
Thr	Thr	Asp	Ala	Cys	Glu	Gly	Lys	Glu	Asn	Phe	Val	Arg	Tyr	Leu	Glu	
490					495					500					505	
cat	gtc	cag	gct	gtc	atc	acg	gtc	aac	gca	acc	aga	aga	gga	gac	ctg	1650
His	Val	Gln	Ala	Val	Ile	Thr	Val	Asn	Ala	Thr	Arg	Arg	Gly	Asp	Leu	
				510					515					520		
aac	atc	aac	atg	act	tcc	cct	atg	ggc	acc	aag	tcc	att	ttg	ctg	agc	1698
Asn	Ile	Asn	Met	Thr	Ser	Pro	Met	Gly	Thr	Lys	Ser	Ile	Leu	Leu	Ser	
			525					530					535			
cgg	cgt	cca	agg	gat	gac	gac	tcc	aag	gtg	ggc	ttt	gac	aag	tgg	cct	1746
Arg	Arg	Pro	Arg	Asp	Asp	Asp	Ser	Lys	Val	Gly	Phe	Asp	Lys	Trp	Pro	
		540					545					550				
ttc	atg	acc	act	cac	acg	tgg	ggg	gaa	gac	gcc	cga	ggc	acc	tgg	acc	1794
Phe	Met	Thr	Thr	His	Thr	Trp	Gly	Glu	Asp	Ala	Arg	Gly	Thr	Trp	Thr	

555 560 565

ctg gag ctg gga ttt gtc ggc agc gcc ccg cag aag ggg gtg ctg aag 1842
 Leu Glu Leu Gly Phe Val Gly Ser Ala Pro Gln Lys Gly Val Leu Lys
 570 575 580 585

gag tgg acc ctg atg ctg cat ggc act cag agt gcc ccg tac atc gac 1890
 Glu Trp Thr Leu Met Leu His Gly Thr Gln Ser Ala Pro Tyr Ile Asp
 590 595 600

cag gtg gtg cgg gat tac cag tcc aag ttg gcc atg tcc aag aaa gag 1938
 Gln Val Val Arg Asp Tyr Gln Ser Lys Leu Ala Met Ser Lys Lys Glu
 605 610 615

gag ctg gag gaa gag ctg gac gaa gcc gtg gag aga agc ctg aaa agc 1986
 Glu Leu Glu Glu Glu Leu Asp Glu Ala Val Glu Arg Ser Leu Lys Ser
 620 625 630

atc ctt aac aag aac tag cgctgcacat ccgcctttcc caccgcctc 2034
 Ile Leu Asn Lys Asn *

635

cctccccagc tccgcctctg tctctgctcc acgtttcagg caggcaccta gcaattccat 2094
 caccgtaca ggcaattccg tcttcttaat ctgaagcttc actcactgtc aatgattatt 2154
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<210> 47
 <211> 638
 <212> PRT
 <213> Homo Sapiens

<400> 47

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 20 25 30
 His Phe Leu Val Glu Leu His Lys Gly Gly Glu Asp Lys Ala Arg Gln
 35 40 45
 Val Ala Ala Glu His Gly Phe Gly Val Arg Lys Leu Pro Phe Ala Glu
 50 55 60
 Gly Leu Tyr His Phe Tyr His Asn Gly Leu Ala Lys Ala Lys Arg Arg
 65 70 75 80
 Arg Ser Leu His His Lys Gln Gln Leu Glu Arg Asp Pro Arg Val Lys
 85 90 95
 Met Ala Leu Gln Gln Glu Gly Phe Asp Arg Lys Lys Arg Gly Tyr Arg
 100 105 110
 Asp Ile Asn Glu Ile Asp Ile Asn Met Asn Asp Pro Leu Phe Thr Lys
 115 120 125
 Gln Trp Tyr Leu Ile Asn Thr Gly Gln Ala Asp Gly Thr Pro Gly Leu
 130 135 140
 Asp Leu Asn Val Ala Glu Ala Trp Glu Leu Gly Tyr Thr Gly Lys Gly
 145 150 155 160
 Val Thr Ile Gly Ile Met Asp Asp Gly Ile Asp Tyr Leu His Pro Asp
 165 170 175
 Leu Ala Ser Asn Tyr Asn Ala Glu Ala Ser Tyr Asp Phe Ser Ser Asn
 180 185 190
 Asp Pro Tyr Pro Tyr Pro Arg Tyr Thr Asp Asp Trp Phe Asn Ser His
 195 200 205
 Gly Thr Arg Cys Ala Gly Glu Val Ser Ala Ala Ala Asn Asn Asn Ile
 210 215 220
 Cys Gly Val Gly Val Ala Tyr Asn Ser Lys Val Ala Gly Ile Arg Met
 225 230 235 240
 Leu Asp Gln Pro Phe Met Thr Asp Ile Ile Glu Ala Ser Ser Ile Ser
 245 250 255
 His Met Pro Gln Leu Ile Asp Ile Tyr Ser Ala Ser Trp Gly Pro Thr
 260 265 270
 Asp Asn Gly Lys Thr Val Asp Gly Pro Arg Asp Val Thr Leu Gln Ala
 275 280 285

Met Ala Asp Gly Val Asn Lys Gly Arg Gly Gly Lys Gly Ser Ile Tyr
 290 295 300
 Val Trp Ala Ser Gly Asp Gly Gly Ser Tyr Asp Asp Cys Asn Cys Asp
 305 310 315 320
 Gly Tyr Ala Ser Ser Met Trp Thr Ile Ser Ile Asn Ser Ala Ile Asn
 325 330 335
 Asp Gly Arg Thr Ala Leu Tyr Asp Glu Ser Cys Ser Ser Thr Leu Ala
 340 345 350
 Ser Thr Phe Ser Asn Gly Arg Lys Arg Asn Pro Glu Ala Gly Val Ala
 355 360 365
 Thr Thr Asp Leu Tyr Gly Asn Cys Thr Leu Arg His Ser Gly Thr Ser
 370 375 380
 Ala Ala Ala Pro Glu Ala Ala Gly Val Phe Ala Leu Ala Leu Glu Ala
 385 390 395 400
 Asn Leu Gly Leu Thr Trp Arg Asp Met Gln His Leu Thr Val Leu Thr
 405 410 415
 Ser Lys Arg Asn Gln Leu His Asp Glu Val His Gln Trp Arg Arg Asn
 420 425 430
 Gly Val Gly Leu Glu Phe Asn His Leu Phe Gly Tyr Gly Val Leu Asp
 435 440 445
 Ala Gly Ala Met Val Lys Met Ala Lys Asp Trp Lys Thr Val Pro Glu
 450 455 460
 Arg Phe His Cys Val Gly Gly Ser Val Gln Asp Pro Glu Lys Ile Pro
 465 470 475 480
 Ser Thr Gly Lys Leu Val Leu Thr Leu Thr Thr Asp Ala Cys Glu Gly
 485 490 495
 Lys Glu Asn Phe Val Arg Tyr Leu Glu His Val Gln Ala Val Ile Thr
 500 505 510
 Val Asn Ala Thr Arg Arg Gly Asp Leu Asn Ile Asn Met Thr Ser Pro
 515 520 525
 Met Gly Thr Lys Ser Ile Leu Leu Ser Arg Arg Pro Arg Asp Asp Asp
 530 535 540
 Ser Lys Val Gly Phe Asp Lys Trp Pro Phe Met Thr Thr His Thr Trp
 545 550 555 560
 Gly Glu Asp Ala Arg Gly Thr Trp Thr Leu Glu Leu Gly Phe Val Gly
 565 570 575
 Ser Ala Pro Gln Lys Gly Val Leu Lys Glu Trp Thr Leu Met Leu His
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 Gly Thr Gln Ser Ala Pro Tyr Ile Asp Gln Val Val Arg Asp Tyr Gln
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 ttc tgt gtc atg gtt ttt gca tct gct gag cga ccg gtc ttc acg aat 96
 Phe Cys Val Met Val Phe Ala Ser Ala Glu Arg Pro Val Phe Thr Asn
 20 25 30
 cat ttt ctt gtg gag ttg cat aaa ggg gga gag gac aaa gct cgc caa 144
 His Phe Leu Val Glu Leu His Lys Gly Gly Glu Asp Lys Ala Arg Gln
 35 40 45
 gtt gca gca gaa cac ggc ttt gga gtc cga aag ctt ccc ttt gct gaa 192

Val	Ala	Ala	Glu	His	Gly	Phe	Gly	Val	Arg	Lys	Leu	Pro	Phe	Ala	Glu		
	50					55					60						
ggt	ctg	tac	cac	ttt	tat	cac	aat	ggc	ctt	gca	aag	gcc	aag	aga	aga	240	
Gly	Leu	Tyr	His	Phe	Tyr	His	Asn	Gly	Leu	Ala	Lys	Ala	Lys	Arg	Arg	80	
65					70				75								
cgc	agc	cta	cac	cac	aag	cag	cag	ctg	gag	aga	gac	ccc	agg	gta	aag	288	
Arg	Ser	Leu	His	His	Lys	Gln	Gln	Leu	Glu	Arg	Asp	Pro	Arg	Val	Lys		
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Met	Ala	Leu	Gln	Gln	Glu	Gly	Phe	Asp	Arg	Lys	Lys	Arg	Gly	Tyr	Arg		
			100					105					110				
gac	atc	aat	gag	atc	gac	atc	aac	atg	aac	gat	cct	ctt	ttt	aca	aag	384	
Asp	Ile	Asn	Glu	Ile	Asp	Ile	Asn	Met	Asn	Asp	Pro	Leu	Phe	Thr	Lys		
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cag	tgg	tat	ctg	atc	aat	act	ggg	caa	gct	gat	ggc	act	cct	ggc	ctt	432	
Gln	Trp	Tyr	Leu	Ile	Asn	Thr	Gly	Gln	Ala	Asp	Gly	Thr	Pro	Gly	Leu		
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gat	ttg	aat	gtg	gct	gaa	gcc	tgg	gag	ctg	gga	tac	aca	ggg	aaa	ggt	480	
Asp	Leu	Asn	Val	Ala	Glu	Ala	Trp	Glu	Leu	Gly	Tyr	Thr	Gly	Lys	Gly		
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Val	Thr	Ile	Gly	Ile	Met	Asp	Asp	Gly	Ile	Asp	Tyr	Leu	His	Pro	Asp		
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ctg	gcc	tcc	aac	tat	aat	gcc	gaa	gca	agt	tac	gac	ttc	agc	agc	aac	576	
Leu	Ala	Ser	Asn	Tyr	Asn	Ala	Glu	Ala	Ser	Tyr	Asp	Phe	Ser	Ser	Asn		
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gac	ccc	tat	cct	tac	cct	cgg	tac	aca	gat	gac	tgg	ttt	aac	agc	cac	624	
Asp	Pro	Tyr	Pro	Tyr	Pro	Arg	Tyr	Thr	Asp	Asp	Trp	Phe	Asn	Ser	His		
		195					200					205					
ggg	acc	cga	tgt	gca	gga	gaa	gtt	tct	gct	gcc	gcc	aac	aac	aat	atc	672	
Gly	Thr	Arg	Cys	Ala	Gly	Glu	Val	Ser	Ala	Ala	Ala	Asn	Asn	Asn	Ile		
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tgt	gga	gtt	gga	gta	gca	tac	aac	tcc	aag	gtt	gca	ggc	atc	cgg	atg	720	
Cys	Gly	Val	Gly	Val	Ala	Tyr	Asn	Ser	Lys	Val	Ala	Gly	Ile	Arg	Met		
225					230					235				240			
ctg	gac	cag	cca	ttc	atg	aca	gac	atc	atc	gag	gcc	tcc	tcc	atc	agt	768	
Leu	Asp	Gln	Pro	Phe	Met	Thr	Asp	Ile	Ile	Glu	Ala	Ser	Ser	Ile	Ser		
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cat	atg	cca	cag	ctg	att	gac	atc	tac	agc	gcc	agc	tgg	ggc	ccc	aca	816	
His	Met	Pro	Gln	Leu	Ile	Asp	Ile	Tyr	Ser	Ala	Ser	Trp	Gly	Pro	Thr		
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gac	aac	ggc	aag	aca	gtg	gat	ggg	ccc	cgg	gac	gtc	acg	ctg	cag	gcc	864	
Asp	Asn	Gly	Lys	Thr	Val	Asp	Gly	Pro	Arg	Asp	Val	Thr	Leu	Gln	Ala		
		275					280					285					
atg	gcc	gat	ggc	gtg	aac	aag	ggc	cgc	ggc	ggc	aaa	ggc	agc	atc	tac	912	
Met	Ala	Asp	Gly	Val	Asn	Lys	Gly	Arg	Gly	Gly	Lys	Gly	Ser	Ile	Tyr		
		290				295					300						
gtg	tgg	gcc	tcc	ggg	gac	ggc	ggc	agc	tat	gac	gac	tgc	aac	tgc	gac	960	
Val	Trp	Ala	Ser	Gly	Asp	Gly	Gly	Ser	Tyr	Asp	Asp	Cys	Asn	Cys	Asp		
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ggc	tac	gcc	tcc	agc	atg	tgg	acc	atc	tcc	atc	aac	tca	gcc	atc	aac	1008	
Gly	Tyr	Ala	Ser	Ser	Met	Trp	Thr	Ile	Ser	Ile	Asn	Ser	Ala	Ile	Asn		

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Asp	Gly	Arg	Thr	Ala	Leu	Tyr	Asp	Glu	Ser	Cys	Ser	Ser	Thr	Leu	Ala														
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Ser	Thr	Phe	Ser	Asn	Gly	Arg	Lys	Arg	Asn	Pro	Glu	Ala	Gly	Val	Ala														
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Thr	Thr	Asp	Leu	Tyr	Gly	Asn	Cys	Thr	Leu	Arg	His	Ser	Gly	Thr	Ser														
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gca	gct	gcc	ccc	gag	gca	gct	ggg	gtg	ttt	gca	ctg	gct	ctg	gag	gct					1200									
Ala	Ala	Ala	Pro	Glu	Ala	Ala	Gly	Val	Phe	Ala	Leu	Ala	Leu	Glu	Ala														
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Asn	Leu	Gly	Leu	Thr	Trp	Arg	Asp	Met	Gln	His	Leu	Thr	Val	Leu	Thr														
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tcc	aaa	cgg	aac	cag	ctt	cac	gac	gag	gtc	cat	cag	tgg	cgg	cgc	aat					1296									
Ser	Lys	Arg	Asn	Gln	Leu	His	Asp	Glu	Val	His	Gln	Trp	Arg	Arg	Asn														
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ggg	gtc	ggc	ctg	gaa	ttt	aat	cac	ctc	ttt	ggc	tac	ggg	gtc	ctt	gat					1344									
Gly	Val	Gly	Leu	Glu	Phe	Asn	His	Leu	Phe	Gly	Tyr	Gly	Val	Leu	Asp														
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gca	ggt	gcc	atg	gtg	aaa	atg	gct	aaa	gac	tgg	aaa	acc	gtg	cct	gag					1392									
Ala	Gly	Ala	Met	Val	Lys	Met	Ala	Lys	Asp	Trp	Lys	Thr	Val	Pro	Glu														
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aga	ttc	cac	tgt	gtg	gga	ggc	tcc	gtg	cag	gac	cct	gag	aaa	ata	cca					1440									
Arg	Phe	His	Cys	Val	Gly	Gly	Ser	Val	Gln	Asp	Pro	Glu	Lys	Ile	Pro														
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Ser	Thr	Gly	Lys	Leu	Val	Leu	Thr	Leu	Thr	Thr	Asp	Ala	Cys	Glu	Gly														
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aag	gaa	aat	ttt	gtc	cgc	tac	ctg	gag	cat	gtc	cag	gct	gtc	atc	acg					1536									
Lys	Glu	Asn	Phe	Val	Arg	Tyr	Leu	Glu	His	Val	Gln	Ala	Val	Ile	Thr														
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gtc	aac	gca	acc	aga	aga	gga	gac	ctg	aac	atc	aac	atg	act	tcc	cct					1584									
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tcc	aag	gtg	ggc	ttt	gac	aag	tgg	cct	ttc	atg	acc	act	cac	acg	tgg					1680									
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Gly	Glu	Asp	Ala	Arg	Gly	Thr	Trp	Thr	Leu	Glu	Leu	Gly	Phe	Val	Gly														
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agc	gcc	ccg	cag	aag	ggg	gtg	ctg	aag	gag	tgg	acc	ctg	atg	ctg	cat					1776									
Ser	Ala	Pro	Gln	Lys	Gly	Val	Leu	Lys	Glu	Trp	Thr	Leu	Met	Leu	His														
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Gly	Thr	Gln	Ser	Ala	Pro	Tyr	Ile	Asp	Gln	Val	Val	Arg	Asp	Tyr	Gln														
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 Ser Lys Leu Ala Met Ser Lys Lys Glu Glu Leu Glu Glu Glu Leu Asp
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gaa gcc gtg gag aga agc ctg aaa agc atc ctt aac aag aac tag 1917
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 Met Thr Ser Tyr Arg Glu Arg Ser Ala Asp Leu Ala
 1 5 10

cgt ttc tac act gtc acc gag ccc cag cga cac ccg agg ggc tac aca 160
 Arg Phe Tyr Thr Val Thr Glu Pro Gln Arg His Pro Arg Gly Tyr Thr
 15 20 25

gta tat aag gtc acc gcc cgg gtt gtt tca cga aga aat cca gag gat 208
 Val Tyr Lys Val Thr Ala Arg Val Val Ser Arg Arg Asn Pro Glu Asp
 30 35 40

gtc cag gag ata att gta tgg aag aga tac agt gat ttt aag aaa cta 256
 Val Gln Glu Ile Ile Val Trp Lys Arg Tyr Ser Asp Phe Lys Lys Leu
 45 50 55 60

cac aaa gaa cta tgg caa att cac aaa aac tta ttc cga cat tca gag 304
 His Lys Glu Leu Trp Gln Ile His Lys Asn Leu Phe Arg His Ser Glu
 65 70 75

ttg ttt cct cca ttt gct aaa gga ata gtg ttt ggg cga ttt gat gaa 352
 Leu Phe Pro Pro Phe Ala Lys Gly Ile Val Phe Gly Arg Phe Asp Glu
 80 85 90

act gtt atc gaa gag aga aga caa tgt gct gaa gac ctg cta cag ttc 400
 Thr Val Ile Glu Glu Arg Arg Gln Cys Ala Glu Asp Leu Leu Gln Phe
 95 100 105

tct gcc aat att cct gct ctt tac aat agt aaa cag ctt gaa gac ttt 448
 Ser Ala Asn Ile Pro Ala Leu Tyr Asn Ser Lys Gln Leu Glu Asp Phe
 110 115 120

ttc aag ggt gga ata att aat gat agt tct gaa tta att ggt cct gct 496
 Phe Lys Gly Gly Ile Ile Asn Asp Ser Ser Glu Leu Ile Gly Pro Ala
 125 130 135 140

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 Glu Gly Phe Ser Ser Asp Ser Asp Leu Val Ser Leu Thr Val Asp Val
 160 165 170

gat tct ctt gct gag tta gat gat gga atg gct tcc aat caa aat tct	640
Asp Ser Leu Ala Glu Leu Asp Asp Gly Met Ala Ser Asn Gln Asn Ser	
175 180 185	
ccc att aga act ttt ggt ctc aat ctt tct tcg gat tct tca gca cta	688
Pro Ile Arg Thr Phe Gly Leu Asn Leu Ser Ser Asp Ser Ser Ala Leu	
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Gly Ala Val Ala Ser Asp Ser Glu Gln Ser Lys Thr Glu Glu Glu Arg	
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gaa agt cgt agc ctc ttt cct ggc agt tta aag ccg aag ctt ggc aag	784
Glu Ser Arg Ser Leu Phe Pro Gly Ser Leu Lys Pro Lys Leu Gly Lys	
225 230 235	
aga gat tat ttg gag aaa gca gga gaa tta ata aag ctg gct tta aaa	832
Arg Asp Tyr Leu Glu Lys Ala Gly Glu Leu Ile Lys Leu Ala Leu Lys	
240 245 250	
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Lys Glu Glu Glu Asp Asp Tyr Glu Ala Ala Ser Asp Phe Tyr Arg Lys	
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gga gtt gat tta ctc cta gaa ggt gtt caa gga gag tca agc cct acc	928
Gly Val Asp Leu Leu Leu Gaa Gly Val Gln Gly Glu Ser Ser Pro Thr	
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Arg Arg Glu Ala Val Lys Arg Arg Thr Ala Glu Tyr Leu Met Arg Ala	
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Glu Ser Ile Ser Ser Leu Tyr Gly Lys Pro Gln Leu Asp Asp Glu Ser	
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Gln Pro Pro Gly Ser Leu Ser Ser Arg Pro Leu Trp Asn Leu Arg Ser	
320 325 330	
cct gcc gag gag ctg aag gcc ttc aga gtc ctt ggg gtg att gac aag	1120
Pro Ala Glu Glu Leu Lys Ala Phe Arg Val Leu Gly Val Ile Asp Lys	
335 340 345	
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Val Leu Leu Val Met Asp Thr Arg Thr Glu Gln Thr Phe Ile Leu Lys	
350 355 360	
ggg cta agg aaa agc agt gaa tac agc agg aac aga aag acc atc atc	1216
Gly Leu Arg Lys Ser Ser Glu Tyr Ser Arg Asn Arg Lys Thr Ile Ile	
365 370 375 380	
ccc cgc tgt gtg ccc aac atg gtg tgt ctg cat aag tac atc atc tct	1264
Pro Arg Cys Val Pro Asn Met Val Cys Leu His Lys Tyr Ile Ile Ser	
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400 405 410	
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Trp Ser Tyr Ile Ser Lys Phe Leu Asn Arg Ser Pro Glu Glu Ser Phe	
415 420 425	
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Asp Ile Lys Glu Val Lys Lys Pro Thr Leu Ala Lys Val His Leu Gln	
430 435 440	

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Gln Pro Thr Ser Ser Pro Gln Asp Ser Ser Ser Phe Glu Ser Arg Gly	
445 450 455 460	
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Ser Asp Gly Gly Ser Met Leu Lys Ala Leu Pro Leu Lys Ser Ser Leu	
465 470 475	
act cca agt tct caa gat gac agc aac cag gaa gat gat ggc caa gat	1552
Thr Pro Ser Ser Gln Asp Asp Ser Asn Gln Glu Asp Asp Gly Gln Asp	
480 485 490	
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Ser Ser Pro Lys Trp Pro Asp Ser Gly Ser Ser Ser Glu Glu Glu Cys	
495 500 505	
act act agt tat tta aca tta tgc aat gaa tat ggg caa gaa aag att	1648
Thr Thr Ser Tyr Leu Thr Leu Cys Asn Glu Tyr Gly Gln Glu Lys Ile	
510 515 520	
gaa cca ggg tct ttg aat gag gag ccc ttc atg aag act gaa ggg aat	1696
Glu Pro Gly Ser Leu Asn Glu Glu Pro Phe Met Lys Thr Glu Gly Asn	
525 530 535 540	
ggt gtt gat aca aaa gct att aaa agc ttc cca gca cac ctt gct gct	1744
Gly Val Asp Thr Lys Ala Ile Lys Ser Phe Pro Ala His Leu Ala Ala	
545 550 555	
gac agt gac agc ccc agc aca cag ctg aga gct cac gag ctg aag ttc	1792
Asp Ser Asp Ser Pro Ser Thr Gln Leu Arg Ala His Glu Leu Lys Phe	
560 565 570	
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Phe Pro Asn Asp Asp Pro Glu Ala Val Ser Ser Pro Arg Thr Ser Asp	
575 580 585	
tcc ctc agt aga tca aaa aat agc ccc atg gaa ttc ttt agg ata gac	1888
Ser Leu Ser Arg Ser Lys Asn Ser Pro Met Glu Phe Phe Arg Ile Asp	
590 595 600	
agt aag gat agc gca agt gaa ctc ctg gga ctt gac ttt gga gaa aaa	1936
Ser Lys Asp Ser Ala Ser Glu Leu Leu Gly Leu Asp Phe Gly Glu Lys	
605 610 615 620	
ttg tat agt cta aaa tca gaa cct ttg aaa cca ttc ttt act ctt cca	1984
Leu Tyr Ser Leu Lys Ser Glu Pro Leu Lys Pro Phe Phe Thr Leu Pro	
625 630 635	
gat gga gac agt gct tct agg agt ttt aat act agt gaa agc aag gta	2032
Asp Gly Asp Ser Ala Ser Arg Ser Phe Asn Thr Ser Glu Ser Lys Val	
640 645 650	
gag ttt aaa gct cag gac acc att agc agg ggc tca gat gac tca gtg	2080
Glu Phe Lys Ala Gln Asp Thr Ile Ser Arg Gly Ser Asp Asp Ser Val	
655 660 665	
cca gtt att tca ttt aaa gat gct gct ttt gat gat gtc agt ggt act	2128
Pro Val Ile Ser Phe Lys Asp Ala Ala Phe Asp Asp Val Ser Gly Thr	
670 675 680	
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Asp Glu Gly Arg Pro Asp Leu Leu Val Asn Leu Pro Gly Glu Leu Glu	
685 690 695 700	
tca aca aga gaa gct gca gca ttg gga cct act aag ttt aca caa act	2224
Ser Thr Arg Glu Ala Ala Ala Leu Gly Pro Thr Lys Phe Thr Gln Thr	
705 710 715	
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Asn	Ile	Gly	Ile	Ile	Glu	Asn	Lys	Leu	Leu	Glu	Ala	Pro	Asp	Val	Leu		
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Cys	Leu	Arg	Leu	Ser	Thr	Glu	Gln	Cys	Gln	Ala	His	Glu	Glu	Lys	Gly		
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ata	gag	gaa	ctg	agt	gat	ccc	tct	ggg	ccc	aaa	tcc	tat	agt	ata	aca	2368	
Ile	Glu	Glu	Leu	Ser	Asp		Ser	Gly	Pro	Lys	Ser	Tyr	Ser	Ile	Thr		
			750			755					760						
gag	aaa	cac	tat	gca	cag	gag	gat	ccc	agg	atg	tta	ttt	gta	gca	gct	2416	
Glu	Lys	His	Tyr	Ala	Gln	Glu	Asp	Pro	Arg	Met	Leu	Phe	Val	Ala	Ala		780
					770				775								
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Val	Asp	His	Ser	Ser	Ser	Gly	Asp	Met	Ser	Leu	Leu	Pro	Ser	Ser	Asp		
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Pro	Lys	Phe	Gln	Gly	Leu	Gly	Val	Val	Glu	Ser	Ala	Val	Thr	Ala	Asn		
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aac	aca	gaa	gaa	agc	tta	ttc	cgt	att	tgt	agt	cca	ctc	tca	ggg	gct	2560	
Asn	Thr	Glu	Glu	Ser	Leu	Phe	Arg	Ile	Cys	Ser	Pro	Leu	Ser	Gly	Ala		
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Asn	Glu	Tyr	Ile	Ala	Ser	Thr	Asp	Thr	Leu	Lys	Thr	Glu	Glu	Val	Leu		
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ctg	ttt	aca	gat	cag	act	gat	gat	ttg	gct	aaa	gag	gaa	cca	act	tct	2656	
Leu	Phe	Thr	Asp	Gln	Thr	Asp	Asp	Leu	Ala	Lys	Glu	Glu	Pro	Thr	Ser		860
					850				855								
tta	ttc	cag	aga	gac	tct	gag	act	aag	ggg	gaa	agt	ggg	tta	gtg	cta	2704	
Leu	Phe	Gln	Arg	Asp	Ser	Glu	Thr	Lys	Gly	Glu	Ser	Gly	Leu	Val	Leu		
				865					870					875			
gaa	gga	gac	aag	gaa	ata	cat	cag	att	ttt	gag	gac	ctt	gat	aaa	aaa	2752	
Glu	Gly	Asp	Lys	Glu	Ile	His	Gln	Ile	Phe	Glu	Asp	Leu	Asp	Lys	Lys		
			880					885					890				
tta	gca	cta	gcc	tcc	agg	ttt	tac	atc	cca	gag	ggc	tgc	att	caa	aga	2800	
Leu	Ala	Leu	Ala	Ser	Arg	Phe	Tyr	Ile	Pro	Glu	Gly	Cys	Ile	Gln	Arg		
			895				900					905					
tgg	gca	gct	gaa	atg	gtg	gta	gcc	ctt	gat	gct	tta	cat	aga	gag	gga	2848	
Trp	Ala	Ala	Glu	Met	Val	Val	Ala	Leu	Asp	Ala	Leu	His	Arg	Glu	Gly		
			910			915					920						
att	gtg	tgc	cgc	gat	ttg	aac	cca	aac	aac	atc	tta	ttg	aat	gat	aga	2896	
Ile	Val	Cys	Arg	Asp	Leu	Asn	Pro	Asn	Asn	Ile	Leu	Leu	Asn	Asp	Arg		940
					930					935							
gga	cac	att	cag	cta	acg	tat	ttt	agc	agg	tgg	agt	gag	gtt	gaa	gat	2944	
Gly	His	Ile	Gln	Leu	Thr	Tyr	Phe	Ser	Arg	Trp	Ser	Glu	Val	Glu	Asp		
				945					950					955			
tcc	tgt	gac	agc	gat	gcc	ata	gag	aga	atg	tac	tgt	gcc	cca	gag	gtt	2992	
Ser	Cys	Asp	Ser	Asp	Ala	Ile	Glu	Arg	Met	Tyr	Cys	Ala	Pro	Glu	Val		
				960				965					970				
gga	gca	atc	act	gaa	gaa	act	gaa	gcc	tgt	gat	tgg	tgg	agt	ttg	ggg	3040	
Gly	Ala	Ile	Thr	Glu	Glu	Thr	Glu	Ala	Cys	Asp	Trp	Trp	Ser	Leu	Gly		
			975				980					985					
gct	gtc	ctc	ttt	gaa	ctt	ctc	act	ggc	aag	act	ctg	gtt	gaa	tgc	cat	3088	
Ala	Val	Leu	Phe	Glu	Leu	Leu	Thr	Gly	Lys	Thr	Leu	Val	Glu	Cys	His		

990 995 1000

cca gca gga ata aat act cac act act ttg aac atg cca gaa tgt gtc 3136
 Pro Ala Gly Ile Asn Thr His Thr Thr Leu Asn Met Pro Glu Cys Val
 1005 1010 1015 1020

tct gaa gag gct cgc tca ctc att caa cag ctc ttg cag ttc aat cct 3184
 Ser Glu Glu Ala Arg Ser Leu Ile Gln Gln Leu Leu Gln Phe Asn Pro
 1025 1030 1035

ctg gaa cga ctt ggt gct gga gtt gct ggt gtt gaa gat atc aaa tct 3232
 Leu Glu Arg Leu Gly Ala Gly Val Ala Gly Val Glu Asp Ile Lys Ser
 1040 1045 1050

cat cca ttt ttt acc cct gtg gat tgg gca gaa ctg atg aga tga 3277
 His Pro Phe Phe Thr Pro Val Asp Trp Ala Glu Leu Met Arg *
 1055 1060 1065

acgtaatgca ggggttatctt cacacattct gatcttctct gtgacaggca tctccagcac 3337
 tgaggcacct ctgactcaca gttacttatg gagcaccaaa gcatttggat aaagaccgtt 3397
 ataggaaatg ggggggaaat ggctaaaaga gaacaattcg tttacaatta caagatatta 3457
 gctaattgtg ccaggggctg ttatatacat atatacacaa ccaaggtgtg atctgaattt 3517
 aatccacatt tgggtgtgca gatgagttgt aaagccaact gaaagagttc cttcaagaag 3577
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 Thr Ala Arg Val Val Ser Arg Arg Asn Pro Glu Asp Val Gln Glu Ile
 35 40 45
 Ile Val Trp Lys Arg Tyr Ser Asp Phe Lys Lys Leu His Lys Glu Leu
 50 55 60
 Trp Gln Ile His Lys Asn Leu Phe Arg His Ser Glu Leu Phe Pro Pro
 65 70 75 80
 Phe Ala Lys Gly Ile Val Phe Gly Arg Phe Asp Glu Thr Val Ile Glu
 85 90 95
 Glu Arg Arg Gln Cys Ala Glu Asp Leu Leu Gln Phe Ser Ala Asn Ile
 100 105 110
 Pro Ala Leu Tyr Asn Ser Lys Gln Leu Glu Asp Phe Phe Lys Gly Gly
 115 120 125
 Ile Ile Asn Asp Ser Ser Glu Leu Ile Gly Pro Ala Glu Ala His Ser
 130 135 140
 Asp Ser Leu Ile Asp Thr Phe Pro Glu Cys Ser Thr Glu Gly Phe Ser
 145 150 155 160
 Ser Asp Ser Asp Leu Val Ser Leu Thr Val Asp Val Asp Ser Leu Ala
 165 170 175
 Glu Leu Asp Asp Gly Met Ala Ser Asn Gln Asn Ser Pro Ile Arg Thr
 180 185 190
 Phe Gly Leu Asn Leu Ser Ser Asp Ser Ser Ala Leu Gly Ala Val Ala
 195 200 205
 Ser Asp Ser Glu Gln Ser Lys Thr Glu Glu Glu Arg Glu Ser Arg Ser
 210 215 220
 Leu Phe Pro Gly Ser Leu Lys Pro Lys Leu Gly Lys Arg Asp Tyr Leu
 225 230 235 240
 Glu Lys Ala Gly Glu Leu Ile Lys Leu Ala Leu Lys Lys Glu Glu Glu
 245 250 255
 Asp Asp Tyr Glu Ala Ala Ser Asp Phe Tyr Arg Lys Gly Val Asp Leu
 260 265 270
 Leu Leu Glu Gly Val Gln Gly Glu Ser Ser Pro Thr Arg Arg Glu Ala
 275 280 285
 Val Lys Arg Arg Thr Ala Glu Tyr Leu Met Arg Ala Glu Ser Ile Ser

290	295	300
Ser Leu Tyr Gly Lys	Pro Gln Leu Asp Asp	Glu Ser Gln Pro Pro Gly
305	310	315
Ser Leu Ser Ser Arg	Pro Leu Trp Asn Leu Arg	Ser Pro Ala Glu Glu
	325	330
Leu Lys Ala Phe Arg	Val Leu Gly Val Ile	Asp Lys Val Leu Leu Val
	340	345
Met Asp Thr Arg Thr	Glu Gln Thr Phe Ile	Leu Lys Gly Leu Arg Lys
	355	360
Ser Ser Glu Tyr Ser	Arg Asn Arg Lys Thr	Ile Ile Pro Arg Cys Val
	370	375
Pro Asn Met Val Cys	Leu His Lys Tyr Ile	Ile Ser Glu Glu Ser Val
385	390	395
Phe Leu Val Leu Gln	His Ala Glu Gly Gly	Lys Leu Trp Ser Tyr Ile
	405	410
Ser Lys Phe Leu Asn	Arg Ser Pro Glu Glu	Ser Phe Asp Ile Lys Glu
	420	425
Val Lys Lys Pro Thr	Leu Ala Lys Val His	Leu Gln Gln Pro Thr Ser
	435	440
Ser Pro Gln Asp Ser	Ser Ser Ser Phe Glu	Ser Arg Gly Ser Asp Gly Gly
	450	455
Ser Met Leu Lys Ala	Leu Pro Leu Lys Ser	Ser Ser Leu Thr Pro Ser Ser
465	470	475
Gln Asp Asp Ser Asn	Gln Glu Asp Asp Gly	Gln Asp Ser Ser Pro Lys
	485	490
Trp Pro Asp Ser Gly	Ser Ser Ser Glu Glu	Glu Cys Thr Thr Ser Tyr
	500	505
Leu Thr Leu Cys Asn	Glu Tyr Gly Gln Glu	Lys Ile Glu Pro Gly Ser
	515	520
Leu Asn Glu Glu Pro	Phe Met Lys Thr Glu	Gly Asn Gly Val Asp Thr
	530	535
Lys Ala Ile Lys Ser	Phe Pro Ala His Leu	Ala Ala Asp Ser Asp Ser
545	550	555
Pro Ser Thr Gln Leu	Arg Ala His Glu Leu	Lys Phe Phe Pro Asn Asp
	565	570
Asp Pro Glu Ala Val	Ser Ser Pro Arg Thr	Ser Asp Ser Leu Ser Arg
	580	585
Ser Lys Asn Ser Pro	Met Glu Phe Phe Arg	Ile Asp Ser Lys Asp Ser
	595	600
Ala Ser Glu Leu Leu	Gly Leu Asp Phe Gly	Glu Lys Leu Tyr Ser Leu
	610	615
Lys Ser Glu Pro Leu	Lys Pro Phe Phe Thr	Leu Pro Asp Gly Asp Ser
625	630	635
Ala Ser Arg Ser Phe	Asn Thr Ser Glu Ser	Lys Val Glu Phe Lys Ala
	645	650
Gln Asp Thr Ile Ser	Arg Gly Ser Asp Asp	Ser Val Pro Val Ile Ser
	660	665
Phe Lys Asp Ala Ala	Phe Asp Asp Val Ser	Gly Thr Asp Glu Gly Arg
	675	680
Pro Asp Leu Leu Val	Asn Leu Pro Gly Glu	Leu Glu Ser Thr Arg Glu
	690	695
Ala Ala Ala Leu Gly	Pro Thr Lys Phe Thr	Gln Thr Asn Ile Gly Ile
705	710	715
Ile Glu Asn Lys Leu	Leu Glu Ala Pro Asp	Val Leu Cys Leu Arg Leu
	725	730
Ser Thr Glu Gln Cys	Gln Ala His Glu Glu	Lys Gly Ile Glu Glu Leu
	740	745
Ser Asp Pro Ser Gly	Pro Lys Ser Tyr Ser	Ile Thr Glu Lys His Tyr
	755	760
Ala Gln Glu Asp Pro	Arg Met Leu Phe Val	Ala Ala Val Asp His Ser
	770	775
Ser Ser Gly Asp Met	Ser Leu Leu Pro Ser	Ser Asp Pro Lys Phe Gln
785	790	795
Gly Leu Gly Val Val	Glu Ser Ala Val Thr	Ala Asn Asn Thr Glu Glu
	805	810
Ser Leu Phe Arg Ile	Cys Ser Pro Leu Ser	Gly Ala Asn Glu Tyr Ile
	820	825
Ala Ser Thr Asp Thr	Leu Lys Thr Glu	Glu Val Leu Leu Phe Thr Asp
	835	840
		845

Gln Thr Asp Asp Leu Ala Lys Glu Glu Pro Thr Ser Leu Phe Gln Arg
 850 855 860
 Asp Ser Glu Thr Lys Gly Glu Ser Gly Leu Val Leu Glu Gly Asp Lys
 865 870 875 880
 Glu Ile His Gln Ile Phe Glu Asp Leu Asp Lys Lys Leu Ala Leu Ala
 885 890 895
 Ser Arg Phe Tyr Ile Pro Glu Gly Cys Ile Gln Arg Trp Ala Ala Glu
 900 905 910
 Met Val Val Ala Leu Asp Ala Leu His Arg Glu Gly Ile Val Cys Arg
 915 920 925
 Asp Leu Asn Pro Asn Asn Ile Leu Leu Asn Asp Arg Gly His Ile Gln
 930 935 940
 Leu Thr Tyr Phe Ser Arg Trp Ser Glu Val Glu Asp Ser Cys Asp Ser
 945 950 955 960
 Asp Ala Ile Glu Arg Met Tyr Cys Ala Pro Glu Val Gly Ala Ile Thr
 965 970 975
 Glu Glu Thr Glu Ala Cys Asp Trp Trp Ser Leu Gly Ala Val Leu Phe
 980 985 990
 Glu Leu Leu Thr Gly Lys Thr Leu Val Glu Cys His Pro Ala Gly Ile
 995 1000 1005
 Asn Thr His Thr Thr Leu Asn Met Pro Glu Cys Val Ser Glu Glu Ala
 1010 1015 1020
 Arg Ser Leu Ile Gln Gln Leu Leu Gln Phe Asn Pro Leu Glu Arg Leu
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 1045 1050 1055
 Thr Pro Val Asp Trp Ala Glu Leu Met Arg
 1060 1065

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 gtc acc gag ccc cag cga cac ccg agg ggc tac aca gta tat aag gtc 96
 Val Thr Glu Pro Gln Arg His Pro Arg Gly Tyr Thr Val Tyr Lys Val
 20 25 30
 acc gcc cgg gtt gtt tca cga aga aat cca gag gat gtc cag gag ata 144
 Thr Ala Arg Val Val Ser Arg Arg Asn Pro Glu Asp Val Gln Glu Ile
 35 40 45
 att gta tgg aag aga tac agt gat ttt aag aaa cta cac aaa gaa cta 192
 Ile Val Trp Lys Arg Tyr Ser Asp Phe Lys Lys Leu His Lys Glu Leu
 50 55 60
 tgg caa att cac aaa aac tta ttc cga cat tca gag ttg ttt cct cca 240
 Trp Gln Ile His Lys Asn Leu Phe Arg His Ser Glu Leu Phe Pro Pro
 65 70 75 80
 ttt gct aaa gga ata gtg ttt ggg cga ttt gat gaa act gtt atc gaa 288
 Phe Ala Lys Gly Ile Val Phe Gly Arg Phe Asp Glu Thr Val Ile Glu
 85 90 95
 gag aga aga caa tgt gct gaa gac ctg cta cag ttc tct gcc aat att 336
 Glu Arg Arg Gln Cys Ala Glu Asp Leu Leu Gln Phe Ser Ala Asn Ile
 100 105 110
 cct gct ctt tac aat agt aaa cag ctt gaa gac ttt ttc aag ggt gga 384

Pro	Ala	Leu	Tyr	Asn	Ser	Lys	Gln	Leu	Glu	Asp	Phe	Phe	Lys	Gly	Gly	
		115					120					125				
ata	att	aat	gat	agt	tct	gaa	tta	att	ggg	cct	gct	gaa	gct	cac	tca	432
Ile	Ile	Asn	Asp	Ser	Ser	Glu	Leu	Ile	Gly	Pro	Ala	Glu	Ala	His	Ser	
		130				135				140						
gat	tcc	ctc	att	gat	acc	ttt	cct	gag	tgt	agt	acg	gaa	ggc	ttc	tcc	480
Asp	Ser	Leu	Ile	Asp	Thr	Phe	Pro	Glu	Cys	Ser	Thr	Glu	Gly	Phe	Ser	
		145			150				155						160	
agt	gac	agt	gat	ctg	gta	tct	ctt	act	gtt	gat	gtg	gat	tct	ctt	gct	528
Ser	Asp	Ser	Asp	Leu	Val	Ser	Leu	Thr	Val	Asp	Val	Asp	Ser	Ser	Leu	
				165					170						175	
gag	tta	gat	gat	gga	atg	gct	tcc	aat	caa	aat	tct	ccc	att	aga	act	576
Glu	Leu	Asp	Asp	Gly	Met	Ala	Ser	Asn	Gln	Asn	Ser	Pro	Ile	Arg	Thr	
				180				185					190			
ttt	ggg	ctc	aat	ctt	tct	tcg	gat	tct	tca	gca	cta	ggg	gct	gtt	gct	624
Phe	Gly	Leu	Asn	Leu	Ser	Ser	Asp	Ser	Ser	Ala	Leu	Gly	Ala	Val	Ala	
		195					200					205				
tct	gac	agt	gaa	cag	agc	aaa	aca	gaa	gaa	gaa	cgg	gaa	agt	cgt	agc	672
Ser	Asp	Ser	Glu	Gln	Ser	Lys	Thr	Glu	Glu	Glu	Arg	Glu	Ser	Arg	Ser	
		210				215					220					
ctc	ttt	cct	ggc	agt	tta	aag	ccg	aag	ctt	ggc	aag	aga	gat	tat	ttg	720
Leu	Phe	Pro	Gly	Ser	Leu	Lys	Pro	Lys	Leu	Gly	Lys	Arg	Asp	Tyr	Leu	
		225			230					235					240	
gag	aaa	gca	gga	gaa	tta	ata	aag	ctg	gct	tta	aaa	aag	gaa	gaa	gaa	768
Glu	Lys	Ala	Gly	Glu	Leu	Ile	Lys	Leu	Ala	Leu	Lys	Lys	Glu	Glu	Glu	
				245					250					255		
gac	gac	tat	gaa	gct	gct	tct	gat	ttt	tat	agg	aag	gga	gtt	gat	tta	816
Asp	Asp	Tyr	Glu	Ala	Ala	Ser	Asp	Phe	Tyr	Arg	Lys	Gly	Val	Asp	Leu	
			260					265					270			
ctc	cta	gaa	ggg	gtt	caa	gga	gag	tca	agc	cct	acc	cgt	cga	gaa	gct	864
Leu	Leu	Glu	Gly	Val	Gln	Gly	Glu	Ser	Ser	Pro	Thr	Arg	Arg	Glu	Ala	
		275					280					285				
gtg	aag	aga	aga	aca	gcc	gag	tac	ctc	atg	cgg	gca	gaa	agt	atc	tct	912
Val	Lys	Arg	Arg	Thr	Ala	Glu	Tyr	Leu	Met	Arg	Ala	Glu	Ser	Ile	Ser	
		290				295					300					
agt	ctt	tat	ggg	aaa	cct	cag	ctt	gat	gat	gaa	tct	cag	cct	cca	gga	960
Ser	Leu	Tyr	Gly	Lys	Pro	Gln	Leu	Asp	Asp	Glu	Ser	Gln	Pro	Pro	Gly	
		305			310					315					320	
tca	cta	agt	tca	agg	ccc	ctt	tgg	aac	cta	agg	agc	cct	gcc	gag	gag	1008
Ser	Leu	Ser	Ser	Arg	Pro	Leu	Trp	Asn	Leu	Arg	Ser	Pro	Ala	Glu	Glu	
				325					330					335		
ctg	aag	gcc	ttc	aga	gtc	ctt	ggg	gtg	att	gac	aag	gtt	tta	ctt	gta	1056
Leu	Lys	Ala	Phe	Arg	Val	Leu	Gly	Val	Ile	Asp	Lys	Val	Leu	Leu	Val	
			340					345					350			
atg	gac	aca	agg	aca	gaa	cag	act	ttc	att	tta	aaa	ggg	cta	agg	aaa	1104
Met	Asp	Thr	Arg	Thr	Glu	Gln	Thr	Phe	Ile	Leu	Lys	Gly	Leu	Arg	Lys	
			355				360					365				
agc	agt	gaa	tac	agc	agg	aac	aga	aag	acc	atc	atc	ccc	cgc	tgt	gtg	1152
Ser	Ser	Glu	Tyr	Ser	Arg	Asn	Arg	Lys	Thr	Ile	Ile	Pro	Arg	Cys	Val	
		370				375					380					
ccc	aac	atg	gtg	tgt	ctg	cat	aag	tac	atc	atc	tct	gag	gag	tca	gta	1200
Pro	Asn	Met	Val	Cys	Leu	His	Lys	Tyr	Ile	Ile	Ser	Glu	Glu	Ser	Val	

385	390	395	400	
ttt ctt gtg ctg Phe Leu Val Leu	cag cat gcg gaa ggt ggc Gln His Ala Glu Gly Gly 405	aaa ctg tgg tca tat atc Lys Leu Trp Ser Tyr Ile 410	1248	
agt aaa ttt cta aac aga agt cct gaa gaa agc ttt gac atc aag gaa Ser Lys Phe Leu Asn Arg Ser Pro Glu Glu Ser Phe Asp Ile Lys Glu 420	425	430	1296	
gtg aaa aaa cct aca ctt gca aaa gtt cac ctg cag cag cca act tct Val Lys Lys Pro Thr Leu Ala Lys Val His Leu Gln Gln Pro Thr Ser 435	440	445	1344	
agt cct cag gac agc agt agc ttt gaa tcc aga gga agt gat ggt gga Ser Pro Gln Asp Ser Ser Ser Phe Glu Ser Arg Gly Ser Asp Gly Gly 450	455	460	1392	
agc atg ctt aaa gct ctg cct ttg aag agt agt ctt act cca agt tct Ser Met Leu Lys Ala Leu Pro Leu Lys Ser Ser Leu Thr Pro Ser Ser 465	470	475	1440	480
caa gat gac agc aac cag gaa gat gat ggc caa gat agc tct cca aag Gln Asp Asp Ser Asn Gln Glu Asp Asp Gly Gln Asp Ser Ser Pro Lys 485	490	495	1488	
tgg cca gat tct ggt tca agt tca gaa gaa gaa tgt act act agt tat Trp Pro Asp Ser Gly Ser Ser Ser Glu Glu Glu Cys Thr Thr Ser Tyr 500	505	510	1536	
tta aca tta tgc aat gaa tat ggg caa gaa aag att gaa cca ggg tct Leu Thr Leu Cys Asn Glu Tyr Gly Gln Glu Lys Ile Glu Pro Gly Ser 515	520	525	1584	
ttg aat gag gag ccc ttc atg aag act gaa ggg aat ggt gtt gat aca Leu Asn Glu Glu Pro Phe Met Lys Thr Glu Gly Asn Gly Val Asp Thr 530	535	540	1632	
aaa gct att aaa agc ttc cca gca cac ctt gct gct gac agt gac agc Lys Ala Ile Lys Ser Phe Pro Ala His Leu Ala Ala Asp Ser Asp Ser 545	550	555	1680	560
ccc agc aca cag ctg aga gct cac gag ctg aag ttc ttc ccc aac gat Pro Ser Thr Gln Leu Arg Ala His Glu Leu Lys Phe Phe Pro Asn Asp 565	570	575	1728	
gac cca gaa gca gtt agt tct cca aga aca tca gat tcc ctc agt aga Asp Pro Glu Ala Val Ser Ser Pro Arg Thr Ser Asp Ser Leu Ser Arg 580	585	590	1776	
tca aaa aat agc ccc atg gaa ttc ttt agg ata gac agt aag gat agc Ser Lys Asn Ser Pro Met Glu Phe Phe Arg Ile Asp Ser Lys Asp Ser 595	600	605	1824	
gca agt gaa ctc ctg gga ctt gac ttt gga gaa aaa ttg tat agt cta Ala Ser Glu Leu Leu Gly Leu Asp Phe Gly Glu Lys Leu Tyr Ser Leu 610	615	620	1872	
aaa tca gaa cct ttg aaa cca ttc ttt act ctt cca gat gga gac agt Lys Ser Glu Pro Leu Lys Pro Phe Phe Thr Leu Pro Asp Gly Asp Ser 625	630	635	1920	640
gct tct agg agt ttt aat act agt gaa agc aag gta gag ttt aaa gct Ala Ser Arg Ser Phe Asn Thr Ser Glu Ser Lys Val Glu Phe Lys Ala 645	650	655	1968	
cag gac acc att agc agg ggc tca gat gac tca gtg cca gtt att tca Gln Asp Thr Ile Ser Arg Gly Ser Asp Ser Val Pro Val Ile Ser 660	665	670	2016	

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Phe Lys Asp Ala Ala Phe Asp Asp Val Ser Gly Thr Asp Glu Gly Arg	
675 680 685	
cct gat ctt ctt gta aat tta cct ggt gaa ttg gag tca aca aga gaa	2112
Pro Asp Leu Leu Val Asn Leu Pro Gly Glu Leu Ser Thr Arg Glu	
690 695 700	
gct gca gca ttg gga cct act aag ttt aca caa act aat ata ggg ata	2160
Ala Ala Ala Leu Gly Pro Thr Lys Phe Thr Gln Thr Asn Ile Gly Ile	
705 710 715 720	
ata gaa aat aaa ctc ttg gaa gcc cct gat gtt tta tgc ctc agg ctt	2208
Ile Glu Asn Lys Leu Leu Glu Ala Pro Asp Val Leu Cys Leu Arg Leu	
725 730 735	
agt act gaa caa tgc caa gca cat gag gag aaa ggc ata gag gaa ctg	2256
Ser Thr Glu Gln Cys Gln Ala His Glu Glu Lys Gly Ile Glu Glu Leu	
740 745 750	
agt gat ccc tct ggg ccc aaa tcc tat agt ata aca gag aaa cac tat	2304
Ser Asp Pro Ser Gly Pro Lys Ser Tyr Ser Ile Thr Glu Lys His Tyr	
755 760 765	
gca cag gag gat ccc agg atg tta ttt gta gca gct gtt gat cat agt	2352
Ala Gln Glu Asp Pro Arg Met Leu Phe Val Ala Val Asp His Ser	
770 775 780	
agt tca gga gat atg tct ttg tta ccc agc tca gat cct aag ttt caa	2400
Ser Ser Gly Asp Met Ser Leu Leu Pro Ser Ser Asp Pro Lys Phe Gln	
785 790 795 800	
gga ctt gga gtg gtt gag tca gca gta act gca aac aac aca gaa gaa	2448
Gly Leu Gly Val Glu Ser Ala Val Thr Ala Asn Asn Thr Glu Glu	
805 810 815	
agc tta ttc cgt att tgt agt cca ctc tca ggt gct aat gaa tat att	2496
Ser Leu Phe Arg Ile Cys Ser Pro Leu Ser Gly Ala Asn Glu Tyr Ile	
820 825 830	
gca agc aca gac act tta aaa aca gaa gaa gta ttg ctg ttt aca gat	2544
Ala Ser Thr Asp Thr Leu Lys Thr Glu Glu Val Leu Leu Phe Thr Asp	
835 840 845	
cag act gat gat ttg gct aaa gag gaa cca act tct tta ttc cag aga	2592
Gln Thr Asp Asp Leu Ala Lys Glu Glu Pro Thr Ser Leu Phe Gln Arg	
850 855 860	
gac tct gag act aag ggt gaa agt ggt tta gtg cta gaa gga gac aag	2640
Asp Ser Glu Thr Lys Gly Glu Ser Gly Leu Val Leu Glu Gly Asp Lys	
865 870 875 880	
gaa ata cat cag att ttt gag gac ctt gat aaa aaa tta gca cta gcc	2688
Glu Ile His Gln Ile Phe Glu Asp Leu Asp Lys Lys Leu Ala Leu Ala	
885 890 895	
tcc agg ttt tac atc cca gag ggc tgc att caa aga tgg gca gct gaa	2736
Ser Arg Phe Tyr Ile Pro Glu Gly Cys Ile Gln Arg Trp Ala Ala Glu	
900 905 910	
atg gtg gta gcc ctt gat gct tta cat aga gag gga att gtg tgc cgc	2784
Met Val Val Ala Leu Asp Ala Leu His Arg Glu Gly Ile Val Cys Arg	
915 920 925	
gat ttg aac cca aac aac atc tta ttg aat gat aga gga cac att cag	2832
Asp Leu Asn Pro Asn Asn Ile Leu Leu Asn Asp Arg Gly His Ile Gln	
930 935 940	

cta acg tat ttt agc agg tgg agt gag gtt gaa gat tcc tgt gac agc	2880
Leu Thr Tyr Phe Ser Arg Trp Ser Glu Val Glu Asp Ser Cys Asp Ser	
945 950 955 960	
gat gcc ata gag aga atg tac tgt gcc cca gag gtt gga gca atc act	2928
Asp Ala Ile Glu Arg Met Tyr Cys Ala Pro Glu Val Gly Ala Ile Thr	
965 970 975	
gaa gaa act gaa gcc tgt gat tgg tgg agt ttg ggt gct gtc ctc ttt	2976
Glu Glu Thr Glu Ala Cys Asp Trp Trp Ser Leu Gly Ala Val Leu Phe	
980 985 990	
gaa ctt ctc act ggc aag act ctg gtt gaa tgc cat cca gca gga ata	3024
Glu Leu Thr Glu Gly Lys Thr Leu Val Glu Cys His Pro Ala Gly Ile	
995 1000 1005	
aat act cac act act ttg aac atg cca gaa tgt gtc tct gaa gag gct	3072
Asn Thr His Thr Thr Leu Asn Met Pro Glu Cys Val Ser Glu Glu Ala	
1010 1015 1020	
cgc tca ctc att caa cag ctc ttg cag ttc aat cct ctg gaa cga ctt	3120
Arg Ser Leu Ile Gln Gln Leu Leu Gln Phe Asn Pro Leu Glu Arg Leu	
1025 1030 1035 1040	
ggg gct gga gtt gct ggt gtt gaa gat atc aaa tct cat cca ttt ttt	3168
Gly Ala Gly Val Ala Gly Val Glu Asp Ile Lys Ser His Pro Phe Phe	
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acc cct gtg gat tgg gca gaa ctg atg aga tga	3201
Thr Pro Val Asp Trp Ala Glu Leu Met Arg *	
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gat gat gcg ccg ctg ttt tta aat gac acc agc gcc ttt gag ttc tcg	96
Asp Asp Ala Pro Leu Phe Leu Asn Asp Thr Ser Ala Phe Glu Phe Ser	
20 25 30	
gat gag gcg ggg gac gag ggg ctt tct cgg ttc aac aaa ctt cga gtt	144
Asp Glu Ala Gly Asp Glu Gly Leu Ser Arg Phe Asn Lys Leu Arg Val	
35 40 45	
gtg gtg gcc gat gac ggt tcc gaa gcc ccg gaa agg cct gtt aac ggg	192
Val Val Ala Asp Asp Gly Ser Glu Ala Pro Glu Arg Pro Val Asn Gly	
50 55 60	
gcg cac ccg acc ctc cag gcc gac gat gat tcc tta ctg gac caa gac	240
Ala His Pro Thr Leu Gln Ala Asp Asp Asp Ser Leu Leu Asp Gln Asp	
65 70 75 80	
tta cct ttg acc aac agt cag ctg agt ttg aag gtg gac tcc tgt gac	288
Leu Pro Leu Thr Asn Ser Gln Leu Ser Leu Lys Val Asp Ser Cys Asp	
85 90 95	
aac tgc agc aaa cag aga gag ata ctg aag cag aga aag gtg aaa gcc	336
Asn Cys Ser Lys Gln Arg Glu Ile Leu Lys Gln Arg Lys Val Lys Ala	

100					105					110						
agg	ttg	acc	att	gct	gcc	gtt	ctg	tac	ttg	ctt	ttc	atg	att	gga	gaa	384
Arg	Leu	Thr	Ile	Ala	Ala	Val	Leu	Tyr	Leu	Leu	Phe	Met	Ile	Gly	Glu	
		115					120					125				
ctt	gta	ggg	gga	tac	att	gca	aat	agc	cta	gca	atc	atg	aca	gat	gca	432
Leu	Val	Gly	Gly	Tyr	Ile	Ala	Asn	Ser	Leu	Ala	Ile	Met	Thr	Asp	Ala	
	130					135					140					
ctt	cat	atg	tta	act	gac	cta	agc	gcc	atc	ata	ctc	acc	ctg	ctt	gct	480
Leu	His	Met	Leu	Thr	Asp	Leu	Ser	Ala	Ile	Ile	Leu	Thr	Leu	Leu	Ala	
	145				150					155					160	
ttg	tgg	cta	tca	tca	aaa	tca	cca	acc	aaa	aga	ttc	acc	ttt	gga	ttt	528
Leu	Trp	Leu	Ser	Ser	Lys	Ser	Pro	Thr	Lys	Arg	Phe	Thr	Phe	Gly	Phe	
				165					170					175		
cat	cgc	tta	gag	gtt	ttg	tca	gct	atg	att	agt	gtg	ctg	ttg	gtg	tat	576
His	Arg	Leu	Glu	Val	Leu	Ser	Ala	Met	Ile	Ser	Val	Leu	Leu	Val	Tyr	
		180					185						190			
ata	ctt	atg	gga	ttc	ctc	tta	tat	gaa	gct	gtg	caa	aga	act	atc	cat	624
Ile	Leu	Met	Gly	Phe	Leu	Leu	Tyr	Glu	Ala	Val	Gln	Arg	Thr	Ile	His	
		195					200					205				
atg	aac	tat	gaa	ata	aat	gga	gat	ata	atg	ctc	atc	acc	gca	gct	gtt	672
Met	Asn	Tyr	Glu	Ile	Asn	Gly	Asp	Ile	Met	Leu	Ile	Thr	Ala	Ala	Val	
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gga	gtt	gca	gtt	aat	gta	ata	atg	ggg	ttt	ctg	ttg	aac	cag	tct	ggt	720
Gly	Val	Ala	Val	Asn	Val	Ile	Met	Gly	Phe	Leu	Leu	Asn	Gln	Ser	Gly	
	225				230					235					240	
cac	cgt	cac	tcc	cat	tcc	cac	tcc	ctg	cct	tca	aat	tcc	cct	acc	aga	768
His	Arg	His	Ser	His	Ser	His	Ser	Leu	Pro	Ser	Asn	Ser	Pro	Thr	Arg	
				245					250					255		
ggg	tct	ggg	tgt	gaa	cgt	aac	cat	ggg	cag	gat	agc	ctg	gca	gtg	aga	816
Gly	Ser	Gly	Cys	Glu	Arg	Asn	His	Gly	Gln	Asp	Ser	Leu	Ala	Val	Arg	
		260						265					270			
gct	gca	ttt	gta	cat	gct	ttg	gga	gat	ctg	gta	cag	agt	gtt	ggt	gtg	864
Ala	Ala	Phe	Val	His	Ala	Leu	Gly	Asp	Leu	Val	Gln	Ser	Val	Gly	Val	
		275					280					285				
cta	ata	gct	gca	tac	atc	ata	cga	ttc	aag	cca	gaa	tac	aag	att	gct	912
Leu	Ile	Ala	Ala	Tyr	Ile	Ile	Arg	Phe	Lys	Pro	Glu	Tyr	Lys	Ile	Ala	
	290					295					300					
gac	ccc	atc	tgt	aca	tac	gta	ttt	tca	tta	ctt	gtg	gct	ttt	aca	aca	960
Asp	Pro	Ile	Cys	Thr	Tyr	Val	Phe	Ser	Leu	Leu	Val	Ala	Phe	Thr	Thr	
	305				310					315					320	
ttt	cga	atc	ata	tgg	gat	aca	gta	gtt	ata	ata	cta	gaa	ggt	gtg	cca	1008
Phe	Arg	Ile	Ile	Trp	Asp	Thr	Val	Val	Ile	Ile	Leu	Glu	Gly	Val	Pro	
				325					330					335		
agc	cat	ttg	aat	gta	gac	tat	atc	aaa	gaa	gcc	ttg	atg	aaa	ata	gaa	1056
Ser	His	Leu	Asn	Val	Asp	Tyr	Ile	Lys	Glu	Ala	Leu	Met	Lys	Ile	Glu	
			340					345					350			
gat	gta	tat	tca	gtc	gaa	gat	tta	aat	atc	tgg	tct	ctc	act	tca	gga	1104
Asp	Val	Tyr	Ser	Val	Glu	Asp	Leu	Asn	Ile	Trp	Ser	Leu	Thr	Ser	Gly	
		355				360						365				
aaa	tct	act	gcc	ata	gtt	cac	ata	cag	cta	att	cct	gga	agt	tca	tct	1152
Lys	Ser	Thr	Ala	Ile	Val	His	Ile	Gln	Leu	Ile	Pro	Gly	Ser	Ser	Ser	
	370					375					380					

aaa tgg gag gaa gta cag tcc aaa gca aac cat tta tta ttg aac aca 1200
 Lys Trp Glu Glu Val Gln Ser Lys Ala Asn His Leu Leu Leu Asn Thr
 385 390 395 400

ttt ggc atg tat aga tgt act att cag ctt cag agt tac agg caa gaa 1248
 Phe Gly Met Tyr Arg Cys Thr Ile Gln Leu Gln Ser Tyr Arg Gln Glu
 405 410 415

gtg gac aga act tgt gca aat tgt cag agt tct agt ccc taa 1290
 Val Asp Arg Thr Cys Ala Asn Cys Gln Ser Ser Ser Pro *
 420 425

ttttatgtat tgttttagca ttgctgaatt cactttatatt atcctgcagt cacagacttg 1350
 agagcaataa atgcaaacct aaatgagaaa atggaatccc tgacagctgt gtccgtatca 1410
 agcatcagtc tctcaaacag ttgccccagc ctgacagtgc tagtctctgt ttaatggtaa 1470
 aaggagactt tgccataatt ttcagatgaa gatgtttccc aaacactggt tacagaatga 1530
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 20 25 30
 Asp Glu Ala Gly Asp Glu Gly Leu Ser Arg Phe Asn Lys Leu Arg Val
 35 40 45
 Val Val Ala Asp Asp Gly Ser Glu Ala Pro Glu Arg Pro Val Asn Gly
 50 55 60
 Ala His Pro Thr Leu Gln Ala Asp Asp Ser Leu Leu Asp Gln Asp
 65 70 75 80
 Leu Pro Leu Thr Asn Ser Gln Leu Ser Leu Lys Val Asp Ser Cys Asp
 85 90 95
 Asn Cys Ser Lys Gln Arg Glu Ile Leu Lys Gln Arg Lys Val Lys Ala
 100 105 110
 Arg Leu Thr Ile Ala Ala Val Leu Tyr Leu Leu Phe Met Ile Gly Glu
 115 120 125
 Leu Val Gly Gly Tyr Ile Ala Asn Ser Leu Ala Ile Met Thr Asp Ala
 130 135 140
 Leu His Met Leu Thr Asp Leu Ser Ala Ile Ile Leu Thr Leu Leu Ala
 145 150 155 160
 Leu Trp Leu Ser Ser Lys Ser Pro Thr Lys Arg Phe Thr Phe Gly Phe
 165 170 175
 His Arg Leu Glu Val Leu Ser Ala Met Ile Ser Val Leu Leu Val Tyr
 180 185 190
 Ile Leu Met Gly Phe Leu Leu Tyr Glu Ala Val Gln Arg Thr Ile His
 195 200 205
 Met Asn Tyr Glu Ile Asn Gly Asp Ile Met Leu Ile Thr Ala Ala Val
 210 215 220
 Gly Val Ala Val Asn Val Ile Met Gly Phe Leu Leu Asn Gln Ser Gly
 225 230 235 240
 His Arg His Ser His Ser His Ser Leu Pro Ser Asn Ser Pro Thr Arg
 245 250 255
 Gly Ser Gly Cys Glu Arg Asn His Gly Gln Asp Ser Leu Ala Val Arg
 260 265 270
 Ala Ala Phe Val His Ala Leu Gly Asp Leu Val Gln Ser Val Gly Val
 275 280 285
 Leu Ile Ala Ala Tyr Ile Ile Arg Phe Lys Pro Glu Tyr Lys Ile Ala
 290 295 300
 Asp Pro Ile Cys Thr Tyr Val Phe Ser Leu Leu Val Ala Phe Thr Thr
 305 310 315 320
 Phe Arg Ile Ile Trp Asp Thr Val Val Ile Ile Leu Glu Gly Val Pro
 325 330 335
 Ser His Leu Asn Val Asp Tyr Ile Lys Glu Ala Leu Met Lys Ile Glu
 340 345 350

Asp Val Tyr Ser Val Glu Asp Leu Asn Ile Trp Ser Leu Thr Ser Gly
 355 360 365
 Lys Ser Thr Ala Ile Val His Ile Gln Leu Ile Pro Gly Ser Ser Ser
 370 375 380
 Lys Trp Glu Glu Val Gln Ser Lys Ala Asn His Leu Leu Leu Asn Thr
 385 390 395 400
 Phe Gly Met Tyr Arg Cys Thr Ile Gln Leu Gln Ser Tyr Arg Gln Glu
 405 410 415
 Val Asp Arg Thr Cys Ala Asn Cys Gln Ser Ser Ser Pro
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 gat gat gcg ccg ctg ttt tta aat gac acc agc gcc ttt gag ttc tcg 96
 Asp Asp Ala Pro Leu Phe Leu Asn Asp Thr Ser Ala Phe Glu Phe Ser
 20 25 30
 gat gag gcg ggg gac gag ggg ctt tct cgg ttc aac aaa ctt cga gtt 144
 Asp Glu Ala Gly Asp Glu Gly Leu Ser Arg Phe Asn Lys Leu Arg Val
 35 40 45
 gtg gtg gcc gat gac ggt tcc gaa gcc ccg gaa agg cct gtt aac ggg 192
 Val Val Ala Asp Asp Gly Ser Glu Ala Pro Glu Arg Pro Val Asn Gly
 50 55 60
 gcg cac ccg acc ctc cag gcc gac gat gat tcc tta ctg gac caa gac 240
 Ala His Pro Thr Leu Gln Ala Asp Asp Asp Ser Leu Leu Asp Gln Asp
 65 70 75 80
 tta cct ttg acc aac agt cag ctg agt ttg aag gtg gac tcc tgt gac 288
 Leu Pro Leu Thr Asn Ser Gln Leu Ser Leu Lys Val Asp Ser Cys Asp
 85 90 95
 aac tgc agc aaa cag aga gag ata ctg aag cag aga aag gtg aaa gcc 336
 Asn Cys Ser Lys Gln Arg Glu Ile Leu Lys Gln Arg Lys Val Lys Ala
 100 105 110
 agg ttg acc att gct gcc gtt ctg tac ttg ctt ttc atg att gga gaa 384
 Arg Leu Thr Ile Ala Ala Val Leu Tyr Leu Leu Phe Met Ile Gly Glu
 115 120 125
 ctt gta ggt gga tac att gca aat agc cta gca atc atg aca gat gca 432
 Leu Val Gly Gly Tyr Ile Ala Asn Ser Leu Ala Ile Met Thr Asp Ala
 130 135 140
 ctt cat atg tta act gac cta agc gcc atc ata ctc acc ctg ctt gct 480
 Leu His Met Leu Thr Asp Leu Ser Ala Ile Ile Leu Thr Leu Leu Ala
 145 150 155 160
 ttg tgg cta tca tca aaa tca cca acc aaa aga ttc acc ttt gga ttt 528
 Leu Trp Leu Ser Ser Lys Ser Pro Thr Lys Arg Phe Thr Phe Gly Phe
 165 170 175
 cat cgc tta gag gtt ttg tca gct atg att agt gtg ctg ttg gtg tat 576
 His Arg Leu Glu Val Leu Ser Ala Met Ile Ser Val Leu Leu Val Tyr
 180 185 190

ata ctt atg gga ttc ctc tta tat gaa gct gtg caa aga act atc cat	624
Ile Leu Met Gly Phe Leu Leu Tyr Glu Ala Val Gln Arg Thr Ile His	
195 200 205	
atg aac tat gaa ata aat gga gat ata atg ctc atc acc gca gct gtt	672
Met Asn Tyr Glu Ile Asn Gly Asp Ile Met Leu Ile Thr Ala Ala Val	
210 215 220	
gga gtt gca gtt aat gta ata atg ggg ttt ctg ttg aac cag tct ggt	720
Gly Val Ala Val Asn Val Ile Met Gly Phe Leu Leu Asn Gln Ser Gly	
225 230 235 240	
cac cgt cac tcc cat tcc cac tcc ctg cct tca aat tcc cct acc aga	768
His Arg His Ser His Ser His Ser Leu Pro Ser Asn Ser Pro Thr Arg	
245 250 255	
ggt tct ggg tgt gaa cgt aac cat ggg cag gat agc ctg gca gtg aga	816
Gly Ser Gly Cys Glu Arg Asn His Gly Gln Asp Ser Leu Ala Val Arg	
260 265 270	
gct gca ttt gta cat gct ttg gga gat ctg gta cag agt gtt ggt gtg	864
Ala Ala Phe Val His Ala Leu Gly Asp Leu Val Gln Ser Val Gly Val	
275 280 285	
cta ata gct gca tac atc ata cga ttc aag cca gaa tac aag att gct	912
Leu Ile Ala Ala Tyr Ile Ile Arg Phe Lys Pro Glu Tyr Lys Ile Ala	
290 295 300	
gac ccc atc tgt aca tac gta ttt tca tta ctt gtg gct ttt aca aca	960
Asp Pro Ile Cys Thr Tyr Val Phe Ser Leu Val Ala Phe Thr Thr	
305 310 315 320	
ttt cga atc ata tgg gat aca gta gtt ata ata cta gaa ggt gtg cca	1008
Phe Arg Ile Ile Trp Asp Thr Val Val Ile Ile Leu Glu Gly Val Pro	
325 330 335	
agc cat ttg aat gta gac tat atc aaa gaa gcc ttg atg aaa ata gaa	1056
Ser His Leu Asn Val Asp Tyr Ile Lys Glu Ala Leu Met Lys Ile Glu	
340 345 350	
gat gta tat tca gtc gaa gat tta aat atc tgg tct ctc act tca gga	1104
Asp Val Tyr Ser Val Glu Asp Leu Asn Ile Trp Ser Leu Thr Ser Gly	
355 360 365	
aaa tct act gcc ata gtt cac ata cag cta att cct gga agt tca tct	1152
Lys Ser Thr Ala Ile Val His Ile Gln Leu Ile Pro Gly Ser Ser Ser	
370 375 380	
aaa tgg gag gaa gta cag tcc aaa gca aac cat tta tta ttg aac aca	1200
Lys Trp Glu Glu Val Gln Ser Lys Ala Asn His Leu Leu Leu Asn Thr	
385 390 395 400	
ttt ggc atg tat aga tgt act att cag ctt cag agt tac agg caa gaa	1248
Phe Gly Met Tyr Arg Cys Thr Ile Gln Leu Gln Ser Tyr Arg Gln Glu	
405 410 415	
gtg gac aga act tgt gca aat tgt cag agt tct agt ccc taa	1290
Val Asp Arg Thr Cys Ala Asn Cys Gln Ser Ser Ser Pro *	
420 425	

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gcc cgg cgg cca gcc tcg gac atc cgc gtg ttc gcc agc aac tgc tcg 102
 Ala Arg Arg Pro Ala Ser Asp Ile Arg Val Phe Ala Ser Asn Cys Ser 25
 10 15 20

atg cac ggg ctg ggc cac gtc ttc ggg cca ggc agc ctg agc ctg cgc 150
 Met His Gly Leu Gly His Val Phe Gly Pro Gly Ser Leu Ser Leu Arg 40
 30 35

cgg ggg atg tgg gca gcg gcc gtg gtc ctg tca gtg gcc acc ttc ctc 198
 Arg Gly Met Trp Ala Ala Ala Val Val Leu Ser Val Ala Thr Phe Leu 55
 45 50

tac cag gtg gct gag agg gtg cgc tac tac agg gag ttc cac cac cag 246
 Tyr Gln Val Ala Glu Arg Val Arg Tyr Tyr Arg Glu Phe His His Gln 70
 60 65

act gcc ctg gat gag cga gaa agc cac cgg ctc atc ttc ccg gct gtc 294
 Thr Ala Leu Asp Glu Arg Glu Ser His Arg Leu Ile Phe Pro Ala Val 85
 75 80

acc ctg tgc aac atc aac cca ctg cgc cgc tcg cgc cta acg ccc aac 342
 Thr Leu Cys Asn Ile Asn Pro Leu Arg Arg Ser Arg Leu Thr Pro Asn 105
 90 95 100

gac ctg cac tgg gct ggg tct gcg ctg ctg ggc ctg gat ccc gca gag 390
 Asp Leu His Trp Ala Gly Ser Ala Leu Leu Gly Leu Asp Pro Ala Glu 120
 110 115

cac gcc gcc ttc ctg cgc gcc ctg ggc cgg ccc cct gca ccg ccc ggc 438
 His Ala Ala Phe Leu Arg Ala Leu Gly Arg Pro Pro Ala Pro Pro Gly 135
 125 130

ttc atg ccc agt ccc acc ttt gac atg gcg caa ctc tat gcc cgt gct 486
 Phe Met Pro Ser Pro Thr Phe Asp Met Ala Gln Leu Tyr Ala Arg Ala 150
 140 145

ggg cac tcc ctg gat gac atg ctg ctg gac tgt cgc ttc cgt ggc caa 534
 Gly His Ser Leu Asp Asp Met Leu Leu Asp Cys Arg Phe Arg Gly Gln 165
 155 160

cct tgt ggg cct gag aac ttc acc acg atc ttc acc cgg atg gga aag 582
 Pro Cys Gly Pro Glu Asn Phe Thr Thr Ile Phe Thr Arg Met Gly Lys 185
 170 175 180

tgc tac aca ttt aac tct ggc gct gat ggg gca gag ctg ctc acc act 630
 Cys Tyr Thr Phe Asn Ser Gly Ala Asp Gly Ala Glu Leu Leu Thr Thr 200
 190 195

act agg ggt ggc atg ggc aat ggg ctg gac atc atg ctg gac gtg cag 678
 Thr Arg Gly Gly Met Gly Asn Gly Leu Asp Ile Met Leu Asp Val Gln 215
 205 210

cag gag gaa tat cta cct gtg tgg agg gac aat gag gag acc ccg ttt 726
 Gln Glu Glu Tyr Leu Pro Val Trp Arg Asp Asn Glu Glu Thr Pro Phe 230
 220 225

gag gtg ggg atc cga gtg cag atc cac agc cag gag gag ccg ccc atc 774
 Glu Val Gly Ile Arg Val Gln Ile His Ser Gln Glu Glu Pro Pro Ile 245
 235 240

atc gat cag ctg ggc ttg ggg gtg tcc ccg ggc tac cag acc ttt gtt 822

Ile 250	Asp	Gln	Leu	Gly	Leu 255	Gly	Val	Ser	Pro	Gly 260	Tyr	Gln	Thr	Phe	Val 265	
tct	tgc	cag	cag	cag	cag	ctg	agc	ttc	ctg	cca	ccg	ccc	tgg	ggc	gat	870
Ser	Cys	Gln	Gln	Gln	Gln	Leu	Ser	Phe	Leu	Pro	Pro	Pro	Trp	Gly	Asp	
				270					275					280		
tgc	agt	tca	gca	tct	ctg	aac	ccc	aac	tat	gag	cca	gag	ccc	tct	gat	918
Cys	Ser	Ser	Ala	Ser	Leu	Asn	Pro	Asn	Tyr	Glu	Pro	Glu	Pro	Ser	Asp	
			285					290					295			
ccc	cta	ggc	tcc	ccc	agc	ccc	agc	ccc	agc	cct	ccc	tat	acc	ctt	atg	966
Pro	Leu	Gly	Ser	Pro	Ser	Pro	Ser	Pro	Ser	Pro	Pro	Tyr	Thr	Leu	Met	
		300					305					310				
ggg	tgt	cgc	ctg	gcc	tgc	gaa	acc	cgc	tac	gtg	gct	cgg	aag	tgc	ggc	1014
Gly	Cys	Arg	Leu	Ala	Cys	Glu	Thr	Arg	Tyr	Val	Ala	Arg	Lys	Cys	Gly	
	315					320					325					
tgc	cga	atg	gtg	tac	atg	cca	ggc	gac	gtg	cca	gtg	tgc	agc	ccc	cag	1062
Cys	Arg	Met	Val	Tyr	Met	Pro	Gly	Asp	Val	Pro	Val	Cys	Ser	Pro	Gln	
330					335				340						345	
cag	tac	aag	aac	tgt	gcc	cac	ccg	gcc	ata	gat	gcc	atg	ctt	cgc	aag	1110
Gln	Tyr	Lys	Asn	Cys	Ala	His	Pro	Ala	Ile	Asp	Ala	Met	Leu	Arg	Lys	
			350						355					360		
gac	tcg	tgc	gcc	tgc	ccc	aac	ccg	tgc	gcc	agc	acg	cgc	tac	gcc	aag	1158
Asp	Ser	Cys	Ala	Cys	Pro	Asn	Pro	Cys	Ala	Ser	Thr	Arg	Tyr	Ala	Lys	
			365					370					375			
gag	ctc	tcc	atg	gtg	cgg	atc	ccg	agc	cgc	gcc	gcc	gcg	cgc	ttc	ctg	1206
Glu	Leu	Ser	Met	Val	Arg	Ile	Pro	Ser	Arg	Ala	Ala	Ala	Arg	Phe	Leu	
		380					385					390				
gcc	cgg	aag	ctc	aac	cgc	agc	gag	gcc	tac	atc	gcg	gag	aac	gtg	ctg	1254
Ala	Arg	Lys	Leu	Asn	Arg	Ser	Glu	Ala	Tyr	Ile	Ala	Glu	Asn	Val	Leu	
	395					400					405					
gcc	ctg	gac	atc	ttc	ttt	gag	gcc	ctc	aac	tat	gag	acc	gtg	gag	cag	1302
Ala	Leu	Asp	Ile	Phe	Phe	Glu	Ala	Leu	Asn	Tyr	Glu	Thr	Val	Glu	Gln	
410					415					420				425		
aag	aag	gcc	tat	gag	atg	tca	gag	ctg	ctt	ggt	gac	att	ggg	ggc	cag	1350
Lys	Lys	Ala	Tyr	Glu	Met	Ser	Glu	Leu	Leu	Gly	Asp	Ile	Gly	Gly	Gln	
				430					435				440			
atg	ggg	ctg	ttc	atc	ggg	gcc	agc	ctg	ctc	acc	atc	ctc	gag	atc	cta	1398
Met	Gly	Leu	Phe	Ile	Gly	Ala	Ser	Leu	Leu	Thr	Ile	Leu	Glu	Ile	Leu	
			445					450					455			
gac	tac	ctc	tgt	gag	gtg	ttc	cga	gac	aag	gtc	ctg	gga	tat	ttc	tgg	1446
Asp	Tyr	Leu	Cys	Glu	Val	Phe	Arg	Asp	Lys	Val	Leu	Gly	Tyr	Phe	Trp	
		460					465					470				
aac	cga	cag	cac	tcc	caa	agg	cac	tcc	agc	acc	aat	ctg	ctt	cag	gaa	1494
Asn	Arg	Gln	His	Ser	Gln	Arg	His	Ser	Ser	Thr	Asn	Leu	Leu	Gln	Glu	
	475					480					485					
ggg	ctg	ggc	agc	cat	cga	acc	caa	gtt	ccc	cac	ctc	agc	ctg	ggc	ccc	1542
Gly	Leu	Gly	Ser	His	Arg	Thr	Gln	Val	Pro	His	Leu	Ser	Leu	Gly	Pro	
490					495				500					505		
aga	cct	ccc	acc	cct	ccc	tgt	gcc	gtc	acc	aag	act	ctc	tcc	gcc	tcc	1590
Arg	Pro	Pro	Thr	Pro	Pro	Cys	Ala	Val	Thr	Lys	Thr	Leu	Ser	Ala	Ser	
				510					515					520		
cac	cgc	acc	tgc	tac	ctt	gtc	aca	cag	ctc	tag	acctgctgtc	tgtgtcctcg				1643
His	Arg	Thr	Cys	Tyr	Leu	Val	Thr	Gln	Leu	*						

525

530

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 caaataaagt cctaatagcat caaaaaaaaaa aaaaaaaaaa aaa 1746

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 <212> PRT
 <213> Homo Sapiens

<400> 56
 Met Lys Pro Thr Ser Gly Pro Glu Glu Ala Arg Arg Pro Ala Ser Asp
 1 5 10 15
 Ile Arg Val Phe Ala Ser Asn Cys Ser Met His Gly Leu Gly His Val
 20 25 30
 Phe Gly Pro Gly Ser Leu Ser Leu Arg Arg Gly Met Trp Ala Ala Ala
 35 40 45
 Val Val Leu Ser Val Ala Thr Phe Leu Tyr Gln Val Ala Glu Arg Val
 50 55 60
 Arg Tyr Tyr Arg Glu Phe His His Gln Thr Ala Leu Asp Glu Arg Glu
 65 70 75 80
 Ser His Arg Leu Ile Phe Pro Ala Val Thr Leu Cys Asn Ile Asn Pro
 85 90 95
 Leu Arg Arg Ser Arg Leu Thr Pro Asn Asp Leu His Trp Ala Gly Ser
 100 105 110
 Ala Leu Leu Gly Leu Asp Pro Ala Glu His Ala Ala Phe Leu Arg Ala
 115 120 125
 Leu Gly Arg Pro Pro Ala Pro Pro Gly Phe Met Pro Ser Pro Thr Phe
 130 135 140
 Asp Met Ala Gln Leu Tyr Ala Arg Ala Gly His Ser Leu Asp Asp Met
 145 150 155 160
 Leu Leu Asp Cys Arg Phe Arg Gly Gln Pro Cys Gly Pro Glu Asn Phe
 165 170 175
 Thr Thr Ile Phe Thr Arg Met Gly Lys Cys Tyr Thr Phe Asn Ser Gly
 180 185 190
 Ala Asp Gly Ala Glu Leu Leu Thr Thr Thr Arg Gly Gly Met Gly Asn
 195 200 205
 Gly Leu Asp Ile Met Leu Asp Val Gln Gln Glu Glu Tyr Leu Pro Val
 210 215 220
 Trp Arg Asp Asn Glu Glu Thr Pro Phe Glu Val Gly Ile Arg Val Gln
 225 230 235 240
 Ile His Ser Gln Glu Glu Pro Pro Ile Ile Asp Gln Leu Gly Leu Gly
 245 250 255
 Val Ser Pro Gly Tyr Gln Thr Phe Val Ser Cys Gln Gln Gln Leu
 260 265 270
 Ser Phe Leu Pro Pro Pro Trp Gly Asp Cys Ser Ser Ala Ser Leu Asn
 275 280 285
 Pro Asn Tyr Glu Pro Glu Pro Ser Asp Pro Leu Gly Ser Pro Ser Pro
 290 295 300
 Ser Pro Ser Pro Pro Tyr Thr Leu Met Gly Cys Arg Leu Ala Cys Glu
 305 310 315 320
 Thr Arg Tyr Val Ala Arg Lys Cys Gly Cys Arg Met Val Tyr Met Pro
 325 330 335
 Gly Asp Val Pro Val Cys Ser Pro Gln Gln Tyr Lys Asn Cys Ala His
 340 345 350
 Pro Ala Ile Asp Ala Met Leu Arg Lys Asp Ser Cys Ala Cys Pro Asn
 355 360 365
 Pro Cys Ala Ser Thr Arg Tyr Ala Lys Glu Leu Ser Met Val Arg Ile
 370 375 380
 Pro Ser Arg Ala Ala Ala Arg Phe Leu Ala Arg Lys Leu Asn Arg Ser
 385 390 395 400
 Glu Ala Tyr Ile Ala Glu Asn Val Leu Ala Leu Asp Ile Phe Phe Glu
 405 410 415
 Ala Leu Asn Tyr Glu Thr Val Glu Gln Lys Lys Ala Tyr Glu Met Ser
 420 425 430
 Glu Leu Leu Gly Asp Ile Gly Gly Gln Met Gly Leu Phe Ile Gly Ala
 435 440 445
 Ser Leu Leu Thr Ile Leu Glu Ile Leu Asp Tyr Leu Cys Glu Val Phe
 450 455 460

Arg Asp Lys Val Leu Gly Tyr Phe Trp Asn Arg Gln His Ser Gln Arg
 465 470 475 480
 His Ser Ser Thr Asn Leu Leu Gln Glu Gly Leu Gly Ser His Arg Thr
 485 490 495
 Gln Val Pro His Leu Ser Leu Gly Pro Arg Pro Pro Thr Pro Pro Cys
 500 505 510
 Ala Val Thr Lys Thr Leu Ser Ala Ser His Arg Thr Cys Tyr Leu Val
 515 520 525
 Thr Gln Leu
 530

<210> 57
 <211> 1596
 <212> DNA
 <213> Homo Sapiens

<220>
 <221> CDS
 <222> (1)...(1596)

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 Met Lys Pro Thr Ser Gly Pro Glu Glu Ala Arg Arg Pro Ala Ser Asp
 1 5 10 15
 atc cgc gtg ttc gcc agc aac tgc tcg atg cac ggg ctg ggc cac gtc 96
 Ile Arg Val Phe Ala Ser Asn Cys Ser Met His Gly Leu Gly His Val
 20 25 30
 ttc ggg cca ggc agc ctg agc ctg cgc cgg ggg atg tgg gca gcg gcc 144
 Phe Gly Pro Gly Ser Leu Ser Leu Arg Arg Gly Met Trp Ala Ala Ala
 35 40 45
 gtg gtc ctg tca gtg gcc acc ttc ctc tac cag gtg gct gag agg gtg 192
 Val Val Leu Ser Val Ala Thr Phe Leu Tyr Gln Val Ala Glu Arg Val
 50 55 60
 cgc tac tac agg gag ttc cac cac cag act gcc ctg gat gag cga gaa 240
 Arg Tyr Tyr Arg Glu Phe His His Gln Thr Ala Leu Asp Glu Arg Glu
 65 70 75 80
 agc cac cgg ctc atc ttc ccg gct gtc acc ctg tgc aac atc aac cca 288
 Ser His Arg Leu Ile Phe Pro Ala Val Thr Leu Cys Asn Ile Asn Pro
 85 90 95
 ctg cgc cgc tcg cgc cta acg ccc aac gac ctg cac tgg gct ggg tct 336
 Leu Arg Arg Ser Arg Leu Thr Pro Asn Asp Leu His Trp Ala Gly Ser
 100 105 110
 gcg ctg ctg ggc ctg gat ccc gca gag cac gcc gcc ttc ctg cgc gcc 384
 Ala Leu Leu Gly Leu Asp Pro Ala Glu His Ala Ala Phe Leu Arg Ala
 115 120 125
 ctg ggc cgg ccc cct gca ccg ccc ggc ttc atg ccc agt ccc acc ttt 432
 Leu Gly Arg Pro Pro Ala Pro Pro Gly Phe Met Pro Ser Pro Thr Phe
 130 135 140
 gac atg gcg caa ctc tat gcc cgt gct ggg cac tcc ctg gat gac atg 480
 Asp Met Ala Gln Leu Tyr Ala Arg Ala Gly His Ser Leu Asp Asp Met
 145 150 155 160
 ctg ctg gac tgt cgc ttc cgt ggc caa cct tgt ggg cct gag aac ttc 528
 Leu Leu Asp Cys Arg Phe Arg Gly Gln Pro Cys Gly Pro Glu Asn Phe
 165 170 175
 acc acg atc ttc acc cgg atg gga aag tgc tac aca ttt aac tct ggc 576
 Thr Thr Ile Phe Thr Arg Met Gly Lys Cys Tyr Thr Phe Asn Ser Gly
 180 185 190

gct gat ggg gca gag ctg ctc acc act act agg ggt ggc atg ggc aat	624
Ala Asp Gly Ala Glu Leu Leu Thr Thr Thr Arg Gly Gly Met Gly Asn	
195 200 205	
ggg ctg gac atc atg ctg gac gtg cag cag gag gaa tat cta cct gtg	672
Gly Leu Asp Ile Met Leu Asp Val Gln Gln Glu Glu Tyr Leu Pro Val	
210 215 220	
tgg agg gac aat gag gag acc ccg ttt gag gtg ggg atc cga gtg cag	720
Trp Arg Asp Asn Glu Glu Thr Pro Phe Glu Val Gly Ile Arg Val Gln	
225 230 235 240	
atc cac agc cag gag gag ccg ccc atc atc gat cag ctg ggc ttg ggg	768
Ile His Ser Gln Glu Glu Pro Pro Ile Ile Asp Gln Leu Gly Leu Gly	
245 250 255	
gtg tcc ccg ggc tac cag acc ttt gtt tct tgc cag cag cag cag ctg	816
Val Ser Pro Gly Tyr Gln Thr Phe Val Ser Cys Gln Gln Gln Gln Leu	
260 265 270	
agc ttc ctg cca ccg ccc tgg ggc gat tgc agt tca gca tct ctg aac	864
Ser Phe Leu Pro Pro Pro Trp Gly Asp Cys Ser Ser Ala Ser Leu Asn	
275 280 285	
ccc aac tat gag cca gag ccc tct gat ccc cta ggc tcc ccc agc ccc	912
Pro Asn Tyr Glu Pro Glu Pro Ser Asp Pro Leu Gly Ser Pro Ser Pro	
290 295 300	
agc ccc agc cct ccc tat acc ctt atg ggg tgt cgc ctg gcc tgc gaa	960
Ser Pro Ser Pro Pro Tyr Thr Leu Met Gly Cys Arg Leu Ala Cys Glu	
305 310 315 320	
acc cgc tac gtg gct cgg aag tgc ggc tgc cga atg gtg tac atg cca	1008
Thr Arg Tyr Val Ala Arg Lys Cys Gly Cys Arg Met Val Tyr Met Pro	
325 330 335	
ggc gac gtg cca gtg tgc agc ccc cag cag tac aag aac tgt gcc cac	1056
Gly Asp Val Pro Val Cys Ser Pro Gln Gln Tyr Lys Asn Cys Ala His	
340 345 350	
ccg gcc ata gat gcc atg ctt cgc aag gac tgc tgc gcc tgc ccc aac	1104
Pro Ala Ile Asp Ala Met Leu Arg Lys Asp Ser Cys Ala Cys Pro Asn	
355 360 365	
ccg tgc gcc agc acg cgc tac gcc aag gag ctc tcc atg gtg cgg atc	1152
Pro Cys Ala Ser Thr Arg Tyr Ala Lys Glu Leu Ser Met Val Arg Ile	
370 375 380	
ccg agc cgc gcc gcc gcg cgc ttc ctg gcc cgg aag ctc aac cgc agc	1200
Pro Ser Arg Ala Ala Ala Arg Phe Leu Ala Arg Lys Leu Asn Arg Ser	
385 390 395 400	
gag gcc tac atc gcg gag aac gtg ctg gcc ctg gac atc ttc ttt gag	1248
Glu Ala Tyr Ile Ala Glu Asn Val Leu Ala Leu Asp Ile Phe Phe Glu	
405 410 415	
gcc ctc aac tat gag acc gtg gag cag aag aag gcc tat gag atg tca	1296
Ala Leu Asn Tyr Glu Thr Val Glu Gln Lys Lys Ala Tyr Glu Met Ser	
420 425 430	
gag ctg ctt ggt gac att ggg ggc cag atg ggg ctg ttc atc ggg gcc	1344
Glu Leu Leu Gly Asp Ile Gly Gly Gln Met Gly Leu Phe Ile Gly Ala	
435 440 445	
agc ctg ctc acc atc ctc gag atc cta gac tac ctc tgt gag gtg ttc	1392
Ser Leu Leu Thr Ile Leu Glu Ile Leu Asp Tyr Leu Cys Glu Val Phe	
450 455 460	

cga gac aag gtc ctg gga tat ttc tgg aac cga cag cac tcc caa agg 1440
 Arg Asp Lys Val Leu Gly Tyr Phe Trp Asn Arg Gln His Ser Gln Arg
 465 470 475 480
 cac tcc agc acc aat ctg ctt cag gaa ggg ctg ggc agc cat cga acc 1488
 His Ser Ser Thr Asn Leu Leu Gln Glu Gly Leu Gly Ser His Arg Thr
 485 490 495
 caa gtt ccc cac ctc agc ctg ggc ccc aga cct ccc acc cct ccc tgt 1536
 Gln Val Pro His Leu Ser Leu Gly Pro Arg Pro Pro Thr Pro Pro Cys
 500 505 510
 gcc gtc acc aag act ctc tcc gcc tcc cac cgc acc tgc tac ctt gtc 1584
 Ala Val Thr Lys Thr Leu Ser Ala Ser His Arg Thr Cys Tyr Leu Val
 515 520 525
 aca cag ctc tag 1596
 Thr Gln Leu *
 530
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 <211> 1670
 <212> DNA
 <213> Homo Sapiens
 <220>
 <221> CDS
 <222> (69)...(1175)
 <400> 58
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 gcccgacc atg gtc ctt gag gtg agt gac cac caa gtg cta aat gac gcc 110
 Met Val Leu Glu Val Ser Asp His Gln Val Leu Asn Asp Ala
 1 5 10
 gag gtt gcc gcc ctc ctg gag aac ttc agc tct tcc tat gac tat gga 158
 Glu Val Ala Ala Leu Leu Glu Asn Phe Ser Ser Ser Tyr Asp Tyr Gly
 15 20 25 30
 gaa aac gag agt gac tcg tgc tgt acc tcc ccg ccc tgc cca cag gac 206
 Glu Asn Glu Ser Asp Ser Cys Cys Thr Ser Pro Pro Cys Pro Gln Asp
 35 40 45
 ttc agc ctg aac ttc gac cgg gcc ttc ctg cca gcc ctc tac agc ctc 254
 Phe Ser Leu Asn Phe Asp Arg Ala Phe Leu Pro Ala Leu Tyr Ser Leu
 50 55 60
 ctc ttt ctg ctg ggg ctg ctg ggc aac ggc gcg gtg gca gcc gtg ctg 302
 Leu Phe Leu Leu Gly Leu Leu Gly Asn Gly Ala Val Ala Ala Val Leu
 65 70 75
 ctg agc cgg cgg aca gcc ctg agc agc acc gac acc ttc ctg ctc cac 350
 Leu Ser Arg Arg Thr Ala Leu Ser Ser Thr Asp Thr Phe Leu Leu His
 80 85 90
 cta gct gta gca gac acg ctg ctg gtg ctg aca ctg ccg ctc tgg gca 398
 Leu Ala Val Ala Asp Thr Leu Leu Val Leu Thr Leu Pro Leu Trp Ala
 95 100 105 110
 gtg gac gct gcc gtc cag tgg gtc ttt ggc tct ggc ctc tgc aaa gtg 446
 Val Asp Ala Ala Val Gln Trp Val Phe Gly Ser Gly Leu Cys Lys Val
 115 120 125
 gca ggt gcc ctc ttc aac atc aac ttc tac gca gga gcc ctc ctg ctg 494
 Ala Gly Ala Leu Phe Asn Ile Asn Phe Tyr Ala Gly Ala Leu Leu Leu
 130 135 140
 gcc tgc atc agc ttt gac cgc tac ctg aac ata gtt cat gcc acc cag 542

Ala Cys Ile Ser Phe Asp Arg Tyr Leu Asn Ile Val His Ala Thr Gln	
145 150 155	
ctc tac cgc cgg ggg ccc ccg gcc cgc gtg acc ctc acc tgc ctg gct	590
Leu Tyr Arg Arg Gly Pro Ala Arg Val Thr Leu Thr Cys Leu Ala	
160 165 170	
gtc tgg ggg ctc tgc ctg ctt ttc gcc ctc cca gac ttc atc ttc ctg	638
Val Trp Gly Leu Cys Leu Leu Phe Ala Leu Pro Asp Phe Ile Phe Leu	
175 180 185 190	
tcg gcc cac cac gac gag cgc ctc aac gcc acc cac tgc caa tac aac	686
Ser Ala His His Asp Glu Arg Leu Asn Ala Thr His Cys Gln Tyr Asn	
195 200 205	
ttc cca cag gtg ggc cgc acg gct ctg cgg gtg ctg cag ctg gtg gct	734
Phe Pro Gln Val Gly Arg Thr Ala Leu Arg Val Leu Gln Leu Val Ala	
210 215 220	
ggc ttt ctg ctg ccc ctg ctg gtc atg gcc tac tgc tat gcc cac atc	782
Gly Phe Leu Leu Pro Leu Leu Val Met Ala Tyr Cys Tyr Ala His Ile	
225 230 235	
ctg gcc gtg ctg ctg gtt tcc agg ggc cag cgg cgc ctg cgg gcc atg	830
Leu Ala Val Leu Leu Val Ser Arg Gly Gln Arg Arg Leu Arg Ala Met	
240 245 250	
cgg ctg gtg gtg gtg gtc gtg gtg gcc ttt gcc ctc tgc tgg acc ccc	878
Arg Leu Val Val Val Val Val Val Ala Phe Ala Leu Cys Trp Thr Pro	
255 260 265 270	
tat cac ctg gtg gtg ctg gtg gac atc ctc atg gac ctg ggc gct ttg	926
Tyr His Leu Val Val Leu Val Asp Ile Leu Met Asp Leu Gly Ala Leu	
275 280 285	
gcc cgc aac tgt ggc cga gaa agc agg gta gac gtg gcc aag tgc gtc	974
Ala Arg Asn Cys Gly Arg Glu Ser Arg Val Asp Val Ala Lys Ser Val	
290 295 300	
acc tca ggc ctg ggc tac atg cac tgc tgc ctc aac ccg ctg ctc tat	1022
Thr Ser Gly Leu Gly Tyr Met His Cys Cys Leu Asn Pro Leu Leu Tyr	
305 310 315	
gcc ttt gta ggg gtc aag ttc cgg gag cgg atg tgg atg ctg ctc ttg	1070
Ala Phe Val Gly Val Lys Phe Arg Glu Arg Met Trp Met Leu Leu Leu	
320 325 330	
cgc ctg ggc tgc ccc aac cag aga ggg ctc cag agg cag cca tgc tct	1118
Arg Leu Gly Cys Pro Asn Gln Arg Gly Leu Gln Arg Gln Pro Ser Ser	
335 340 345 350	
tcc cgc cgg gat tca tcc tgg tct gag acc tca gag gcc tcc tac tgc	1166
Ser Arg Arg Asp Ser Ser Trp Ser Glu Thr Ser Glu Ala Ser Tyr Ser	
355 360 365	
ggc ttg tga ggccggaatc cgggctcccc tttcgccac agtctgactt	1215
Gly Leu *	

ccccgcattc caggtccttc cctccctctg ccggtctctg ctctcccca tatectcgct	1275
cccgaggactc actggcagcc ccagcaccac caggtctccc gggaagccac cctcccagct	1335
ctgaggactg caccattgct gctccttagc tgccaagccc catcctgccc cccgaggtgg	1395
ctgcctggag ccccaactgcc cttctcatctt ggaaactaaa acttcatctt ccccaagtgc	1455
ggggagtaca aggcattggcg tagagggtgc tgccccatga agccacagcc caggcctcca	1515
gctcagcagt gactgtggcc atggtcccca agacctctat atttgctctt ttatttttat	1575
gtctaaaatc ctgcttaaaa cttttcaata aacaagatcg tcaggaccaa aaaaaaaaaa	1635
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaa	1670

<210> 59

<211> 368
 <212> PRT
 <213> Homo Sapiens

<400> 59
 Met Val Leu Glu Val Ser Asp His Gln Val Leu Asn Asp Ala Glu Val
 1 5 10 15
 Ala Ala Leu Leu Glu Asn Phe Ser Ser Ser Tyr Asp Tyr Gly Glu Asn
 20 25 30
 Glu Ser Asp Ser Cys Cys Thr Ser Pro Pro Cys Pro Gln Asp Phe Ser
 35 40 45
 Leu Asn Phe Asp Arg Ala Phe Leu Pro Ala Leu Tyr Ser Leu Leu Phe
 50 55 60
 Leu Leu Gly Leu Leu Gly Asn Gly Ala Val Ala Val Leu Leu Ser
 65 70 75 80
 Arg Arg Thr Ala Leu Ser Ser Thr Asp Thr Phe Leu Leu His Leu Ala
 85 90 95
 Val Ala Asp Thr Leu Leu Val Leu Thr Leu Pro Leu Trp Ala Val Asp
 100 105 110
 Ala Ala Val Gln Trp Val Phe Gly Ser Gly Leu Cys Lys Val Ala Gly
 115 120 125
 Ala Leu Phe Asn Ile Asn Phe Tyr Ala Gly Ala Leu Leu Ala Cys
 130 135 140
 Ile Ser Phe Asp Arg Tyr Leu Asn Ile Val His Ala Thr Gln Leu Tyr
 145 150 155 160
 Arg Arg Gly Pro Pro Ala Arg Val Thr Leu Thr Cys Leu Ala Val Trp
 165 170 175
 Gly Leu Cys Leu Leu Phe Ala Leu Pro Asp Phe Ile Phe Leu Ser Ala
 180 185 190
 His His Asp Glu Arg Leu Asn Ala Thr His Cys Gln Tyr Asn Phe Pro
 195 200 205
 Gln Val Gly Arg Thr Ala Leu Arg Val Leu Gln Leu Val Ala Gly Phe
 210 215 220
 Leu Leu Pro Leu Leu Val Met Ala Tyr Cys Tyr Ala His Ile Leu Ala
 225 230 235 240
 Val Leu Leu Val Ser Arg Gly Gln Arg Arg Leu Arg Ala Met Arg Leu
 245 250 255
 Val Val Val Val Val Val Ala Phe Ala Leu Cys Trp Thr Pro Tyr His
 260 265 270
 Leu Val Val Leu Val Asp Ile Leu Met Asp Leu Gly Ala Leu Ala Arg
 275 280 285
 Asn Cys Gly Arg Glu Ser Arg Val Asp Val Ala Lys Ser Val Thr Ser
 290 295 300
 Gly Leu Gly Tyr Met His Cys Cys Leu Asn Pro Leu Leu Tyr Ala Phe
 305 310 315 320
 Val Gly Val Lys Phe Arg Glu Arg Met Trp Met Leu Leu Leu Arg Leu
 325 330 335
 Gly Cys Pro Asn Gln Arg Gly Leu Gln Arg Gln Pro Ser Ser Ser Arg
 340 345 350
 Arg Asp Ser Ser Trp Ser Glu Thr Ser Glu Ala Ser Tyr Ser Gly Leu
 355 360 365

<210> 60
 <211> 1107
 <212> DNA
 <213> Homo Sapiens

<220>
 <221> CDS
 <222> (1)...(1107)

<400> 60
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 Met Val Leu Glu Val Ser Asp His Gln Val Leu Asn Asp Ala Glu Val
 1 5 10 15
 gcc gcc ctc ctg gag aac ttc agc tct tcc tat gac tat gga gaa aac 96
 Ala Ala Leu Leu Glu Asn Phe Ser Ser Ser Tyr Asp Tyr Gly Glu Asn

20	25	30	
gag agt gac tgc tgc tgt acc tcc ccg ccc tgc cca cag gac ttc agc Glu Ser Asp Ser Cys Cys Thr Ser Pro Pro Cys Pro Gln Asp Phe Ser 35 40 45			144
ctg aac ttc gac cgg gcc ttc ctg cca gcc ctc tac agc ctc ctc ttt Leu Asn Phe Asp Arg Ala Phe Leu Pro Ala Leu Tyr Ser Leu Leu Phe 50 55 60			192
ctg ctg ggg ctg ctg ggc aac ggc gcg gtg gca gcc gtg ctg ctg agc Leu Leu Gly Leu Leu Gly Asn Gly Ala Val Ala Ala Val Leu Leu Ser 65 70 75 80			240
cgg cgg aca gcc ctg agc agc acc gac acc ttc ctg ctc cac cta gct Arg Arg Thr Ala Leu Ser Ser Thr Asp Thr Phe Leu Leu His Leu Ala 85 90 95			288
gta gca gac acg ctg ctg gtg ctg aca ctg ccg ctc tgg gca gtg gac Val Ala Asp Thr Leu Leu Val Leu Thr Leu Pro Leu Trp Ala Val Asp 100 105 110			336
gct gcc gtc cag tgg gtc ttt ggc tct ggc ctc tgc aaa gtg gca ggt Ala Ala Val Gln Trp Val Phe Gly Ser Gly Leu Cys Lys Val Ala Gly 115 120 125			384
gcc ctc ttc aac atc aac ttc tac gca gga gcc ctc ctg ctg gcc tgc Ala Leu Phe Asn Ile Asn Phe Tyr Ala Gly Ala Leu Leu Leu Ala Cys 130 135 140			432
atc agc ttt gac cgc tac ctg aac ata gtt cat gcc acc cag ctc tac Ile Ser Phe Asp Arg Tyr Leu Asn Ile Val His Ala Thr Gln Leu Tyr 145 150 155 160			480
cgc cgg ggg ccc ccg gcc cgc gtg acc ctc acc tgc ctg gct gtc tgg Arg Arg Gly Pro Pro Ala Arg Val Thr Leu Thr Cys Leu Ala Val Trp 165 170 175			528
ggg ctc tgc ctg ctt ttc gcc ctc cca gac ttc atc ttc ctg tgc gcc Gly Leu Cys Leu Leu Phe Ala Leu Pro Asp Phe Ile Phe Leu Ser Ala 180 185 190			576
cac cac gac gag cgc ctc aac gcc acc cac tgc caa tac aac ttc cca His His Asp Glu Arg Leu Asn Ala Thr His Cys Gln Tyr Asn Phe Pro 195 200 205			624
cag gtg ggc cgc acg gct ctg cgg gtg ctg cag ctg gtg gct ggc ttt Gln Val Gly Arg Thr Ala Leu Arg Val Leu Gln Leu Val Ala Gly Phe 210 215 220			672
ctg ctg ccc ctg ctg gtc atg gcc tac tgc tat gcc cac atc ctg gcc Leu Leu Pro Leu Leu Val Met Ala Tyr Cys Tyr Ala His Ile Leu Ala 225 230 235 240			720
gtg ctg ctg gtt tcc agg ggc cag cgg cgc ctg cgg gcc atg cgg ctg Val Leu Leu Val Ser Arg Gly Gln Arg Arg Leu Arg Ala Met Arg Leu 245 250 255			768
gtg gtg gtg gtc gtg gtg gcc ttt gcc ctc tgc tgg acc ccc tat cac Val Val Val Val Val Val Ala Phe Ala Leu Cys Trp Thr Pro Tyr His 260 265 270			816
ctg gtg gtg ctg gtg gac atc ctc atg gac ctg ggc gct ttg gcc cgc Leu Val Val Leu Val Asp Ile Leu Met Asp Leu Gly Ala Leu Ala Arg 275 280 285			864
aac tgt ggc cga gaa agc agg gta gac gtg gcc aag tgc gtc acc tca Asn Cys Gly Arg Glu Ser Arg Val Asp Val Ala Lys Ser Val Thr Ser 290 295 300			912


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ggc ctg ggc tac atg cac tgc tgc ctc aac ccg ctg ctc tat gcc ttt 960
Gly Leu Gly Tyr Met His Cys Cys Leu Asn Pro Leu Leu Tyr Ala Phe
305 310 315 320

gta ggg gtc aag ttc cgg gag cgg atg tgg atg ctg ctc ttg cgc ctg 1008
Val Gly Val Lys Phe Arg Glu Arg Met Trp Met Leu Leu Leu Arg Leu
325 330 335

ggc tgc ccc aac cag aga ggg ctc cag agg cag cca tgc tct tcc cgc 1056
Gly Cys Pro Asn Gln Arg Gly Leu Gln Arg Gln Pro Ser Ser Ser Arg
340 345 350

cgg gat tca tcc tgg tct gag acc tca gag gcc tcc tac tgc ggc ttg 1104
Arg Asp Ser Ser Trp Ser Glu Thr Ser Glu Ala Ser Tyr Ser Gly Leu
355 360 365

tga 1107
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<210> 61
<211> 3614
<212> DNA
<213> Homo Sapiens
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<220>
<221> CDS
<222> (19)...(2778)
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<400> 61
cctcggcgggc gcccaacg atg acc gct ccc tgg cgg cgc ctc cgg agt ctg 51
Met Thr Ala Pro Trp Arg Arg Leu Arg Ser Leu
1 5 10

gtt tgg gaa tac tgg gcc ggg ctc ctc gtg tgc gcc ttc tgg atc ccg 99
Val Trp Glu Tyr Trp Ala Gly Leu Leu Val Cys Ala Phe Trp Ile Pro
15 20 25

gac tgc cgc ggg atg ccc cac gtc atc cgg atc gga gga atc ttc gag 147
Asp Ser Arg Gly Met Pro His Val Ile Arg Ile Gly Gly Ile Phe Glu
30 35 40

tat gcg gac ggc ccc aac gcc cag gtc atg aat gcc gag gag cat gcc 195
Tyr Ala Asp Gly Pro Asn Ala Gln Val Met Asn Ala Glu Glu His Ala
45 50 55

ttt cga ttt tct gcc aac atc atc aac agg aac agg act ctg ctg ccc 243
Phe Arg Phe Ser Ala Asn Ile Ile Asn Arg Asn Arg Thr Leu Leu Pro
60 65 70 75

aac aca acc ttg acc tat gac ata cag agg att cac ttc cat gac agc 291
Asn Thr Thr Leu Thr Tyr Asp Ile Gln Arg Ile His Phe His Asp Ser
80 85 90

ttc gag gcg acc aaa aag gcc tgt gac cag ctg gca ctg ggc gtg gtg 339
Phe Glu Ala Thr Lys Lys Ala Cys Asp Gln Leu Ala Leu Gly Val Val
95 100 105

gcg atc ttc ggc cca tca cag ggc tcc tgc acc aat gcc gtc cag tcc 387
Ala Ile Phe Gly Pro Ser Gln Gly Ser Cys Thr Asn Ala Val Gln Ser
110 115 120

atc tgc aat gcc ctg gag gtg ccc cac atc cag ctg cgt tgg aag cac 435
Ile Cys Asn Ala Leu Glu Val Pro His Ile Gln Leu Arg Trp Lys His
125 130 135

cac ccg ctg gac aac aag gac acc ttc tac gtg aac ctc tac ccc gac 483
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His 140	Pro	Leu	Asp	Asn 145	Lys	Asp	Thr	Phe	Tyr	Val 150	Asn	Leu	Tyr	Pro	Asp 155	
tac	gcc	tcg	ctc	agc	cat	gcc	atc	ctc	gac	ctg	gtc	cag	tac	ctc	aag	531
Tyr	Ala	Ser	Leu	Ser 160	His	Ala	Ile	Leu	Asp 165	Leu	Val	Gln	Tyr	Leu	Lys 170	
tgg	cgg	tca	gcc	acc	gtg	gtc	tat	gac	gac	agt	aca	ggg	ctc	atc	cga	579
Trp	Arg	Ser	Ala	Thr 175	Val	Val	Tyr	Asp 180	Asp	Ser	Thr	Gly	Leu	Ile	Arg 185	
ctg	cag	gag	ctc	atc	atg	gcc	cca	tca	aga	tac	aac	atc	cgc	ctg	aag	627
Leu	Gln	Glu	Leu	Ile 190	Met	Ala	Pro	Ser 195	Arg	Tyr	Asn	Ile	Arg	Leu	Lys 200	
atc	cgt	cag	ctc	ccc	atc	gac	tct	gac	gac	tcg	cgc	ccc	ttg	ctc	aag	675
Ile	Arg	Gln	Leu	Pro 205	Ile	Asp 210	Ser	Asp	Asp	Ser	Arg	Pro	Leu	Leu	Lys 215	
gag	atg	aag	cga	ggc	cgg	gaa	ttc	cgc	att	atc	ttc	gac	tgc	agc	cac	723
Glu	Met	Lys	Arg	Gly 220	Arg	Glu	Phe	Arg	Ile 225	Ile 230	Phe	Asp	Cys	Ser	His 235	
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Thr	Glu	Tyr	Tyr	His 255	Phe	Ile	Phe	Thr 260	Thr	Leu	Asp	Leu	Tyr	Ala	Leu 265	
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122

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 Tyr Asp Ile Gln Arg Ile His Phe His Asp Ser Phe Glu Ala Thr Lys
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 Ser Gln Gly Ser Cys Thr Asn Ala Val Gln Ser Ile Cys Asn Ala Leu
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 Glu Val Pro His Ile Gln Leu Arg Trp Lys His His Pro Leu Asp Asn
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 Lys Asp Thr Phe Tyr Val Asn Leu Tyr Pro Asp Tyr Ala Ser Leu Ser
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Pro His Val	Ile	Arg	Ile	Gly	Gly	Ile	Phe	Glu	Tyr	Ala	Asp	Gly	Pro			
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Lys Asp Thr	Phe	Tyr	Val	Asn	Leu	Tyr	Pro	Asp	Tyr	Ala	Ser	Leu	Ser			
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His Ala Ile	Leu	Asp	Leu	Val	Gln	Tyr	Leu	Lys	Trp	Arg	Ser	Ala	Thr			
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Val Val Tyr	Asp	Asp	Ser	Thr	Gly	Leu	Ile	Arg	Leu	Gln	Glu	Leu	Ile			
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820 825 830	

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gtc ctc tct gtg ctg gtg gcc gtg ggc gag ttt gtg tac aag ctc cgc 2544
Val Leu Ser Val Leu Val Ala Val Gly Glu Phe Val Tyr Lys Leu Arg
      835                      840                      845

aaa aca gca gag aga gag cag cgt tcc ttc tgc agc acc gtg gcc gat 2592
Lys Thr Ala Glu Arg Glu Gln Arg Ser Phe Cys Ser Thr Val Ala Asp
      850                      855                      860

gag atc cgt ttc tcc ctt acc tgc cag cgt cga gtc aag cac aag cct 2640
Glu Ile Arg Phe Ser Leu Thr Cys Gln Arg Arg Val Lys His Lys Pro
      865                      870                      875                      880

cag cct ccc atg atg gtc aag act gac gcc gtc atc aac atg cac aca 2688
Gln Pro Pro Met Met Val Lys Thr Asp Ala Val Ile Asn Met His Thr
      885                      890                      895

ttc aat gac cgc cgg ctt ccc ggc aag gac agc atg gcc tgc agc aca 2736
Phe Asn Asp Arg Arg Leu Pro Gly Lys Asp Ser Met Ala Cys Ser Thr
      900                      905                      910

tcc tta gcc cct gtg ttc ccc tag 2760
Ser Leu Ala Pro Val Phe Pro *
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      Met Arg Gly Leu Leu Val Leu Ser Val Leu Leu Gly Ala Val
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ttt ggc aag gag gac ttt gtg ggg cat cag gtg ctc cga atc tct gta 97
Phe Gly Lys Glu Asp Phe Val Gly His Gln Val Leu Arg Ile Ser Val
      15                      20                      25                      30

gcc gat gag gcc cag gta cag aag gtg aag gag ctg gag gac ctg gag 145
Ala Asp Glu Ala Gln Val Gln Lys Val Lys Glu Leu Glu Asp Leu Glu
      35                      40                      45

cac ctg cag ctg gac ttc tgg cgg ggg cct gcc cac cct ggc tcc ccc 193
His Leu Gln Leu Asp Phe Trp Arg Gly Pro Ala His Pro Gly Ser Pro
      50                      55                      60

atc gac gtc cga gtg ccc ttc ccc agc atc cag gcg gtc aag atc ttt 241
Ile Asp Val Arg Val Pro Phe Pro Ser Ile Gln Ala Val Lys Ile Phe
      65                      70                      75

ctg gag tcc cac ggc atc agc tat gag acc atg atc gag gac gtg cag 289
Leu Glu Ser His Gly Ile Ser Tyr Glu Thr Met Ile Glu Asp Val Gln
      80                      85                      90

tcg ctg ctg gac gag gag cag gag cag atg ttc gcc ttc cgg tcc cgg 337
Ser Leu Leu Asp Glu Glu Gln Glu Gln Met Phe Ala Phe Arg Ser Arg
      95                      100                      105                      110

gcg cgc tcc acc gac act ttt aac tac gcc acc tac cac acc ctg gag 385
Ala Arg Ser Thr Asp Thr Phe Asn Tyr Ala Thr Tyr His Thr Leu Glu
      115                      120                      125

gag atc tat gac ttc ctg gac ctg ctg gtg gcg gag aac ccg cac ctt 433
Glu Ile Tyr Asp Phe Leu Asp Leu Leu Val Ala Glu Asn Pro His Leu

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130						135					140					
gtc Val	agc Ser	aag Lys 145	atc Ile	cag Gln	att Ile	ggc Gly	aac Asn 150	acc Thr	tat Tyr	gaa Glu	ggg Gly	cgt Arg 155	ccc Pro	att Ile	tat Tyr	481
gtg Val	ctg Leu 160	aag Lys	ttc Phe	agc Ser	acg Thr	ggg Gly 165	ggc Gly	agt Ser	aag Lys	cgt Arg	cca Pro 170	gcc Ala	atc Ile	tgg Trp	atc Ile	529
gac Asp 175	acg Thr	ggc Gly	atc Ile	cat His	tcc Ser 180	cgg Arg	gag Glu	tgg Trp	gtc Val	acc Thr 185	cag Gln	gcc Ala	agt Ser	ggg Gly	gtc Val 190	577
tgg Trp	ttt Phe	gca Ala	aag Lys	aag Lys 195	atc Ile	act Thr	caa Gln	gac Asp	tat Tyr 200	ggg Gly	cag Gln	gat Asp	gca Ala	gct Ala 205	ttc Phe	625
acc Thr	gcc Ala	att Ile	ctc Leu 210	gac Asp	acc Thr	ttg Leu	gac Asp	atc Ile 215	ttc Phe	ctg Leu	gag Glu	atc Ile	gtc Val 220	acc Thr	aac Asn	673
cct Pro	gat Asp	ggc Gly 225	ttt Phe	gcc Ala	ttc Phe	acg Thr	cac His 230	agc Ser	acg Thr	aat Asn	cgc Arg	atg Met 235	tgg Trp	cgc Arg	aag Lys	721
act Thr	cgg Arg 240	tcc Ser	cac His	aca Thr	gca Ala	ggc Gly 245	tcc Ser	ctc Leu	tgt Cys	att Ile	ggc Gly 250	gtg Val	gac Asp	ccc Pro	aac Asn	769
agg Arg 255	aac Asn	tgg Trp	gac Asp	gct Ala	ggc Gly 260	ttt Phe	ggg Gly	ttg Leu	tcc Ser	gga Gly 265	gcc Ala	agc Ser	agt Ser	aac Asn	ccc Pro 270	817
tgc Cys	tcg Ser	gag Glu	act Thr	tac Tyr 275	cac His	ggc Gly	aag Lys	ttt Phe	gcc Ala 280	aat Asn	tcc Ser	gaa Glu	gtg Val	gag Glu 285	gtc Val	865
aag Lys	tcc Ser	att Ile	gta Val 290	gac Asp	ttt Phe	gtg Val	aag Lys	gac Asp 295	cat His	ggg Gly	aac Asn	atc Ile	aag Lys 300	gcc Ala	ttc Phe	913
atc Ile	tcc Ser	atc Ile 305	cac His	agc Ser	tac Tyr	tcc Ser	cag Gln 310	ctc Leu	ctc Leu	atg Met	tat Tyr	ccc Pro 315	tat Tyr	ggc Gly	tac Tyr	961
aaa Lys	aca Thr 320	gaa Glu	cca Pro	gtc Val	cct Pro	gac Asp 325	cag Gln	gat Asp	gag Glu	ctg Leu	gat Asp 330	cag Gln	ctt Leu	tcc Ser	aag Lys	1009
gct Ala 335	gct Ala	gtg Val	aca Thr	gcc Ala	ctg Leu 340	ggc Ala	tct Ser	ctc Leu	tac Tyr	ggg Gly 345	acc Thr	aag Lys	ttc Phe	aac Asn	tat Tyr 350	1057
ggc Gly	agc Ser	atc Ile	atc Ile	aag Lys 355	gca Ala	att Ile	tat Tyr	caa Gln	gcc Ala 360	agt Ser	gga Gly	agc Ser	act Thr	att Ile	gac Asp 365	1105
tgg Trp	acc Thr	tac Tyr	agc Ser	cag Gln 370	ggc Gly	atc Ile	aag Lys	tac Tyr 375	tcc Ser	ttc Phe	acc Thr	ttc Phe	gag Glu 380	ctc Leu	cgg Arg	1153
gac Asp	act Thr	ggg Gly 385	cgc Arg	tat Tyr	ggc Gly	ttc Phe	ctg Leu 390	ctg Leu	cca Pro	gcc Ala	tcc Ser	cag Gln 395	atc Ile	atc Ile	ccc Pro	1201
aca Thr	gcc Ala 400	aag Lys	gag Glu	acg Thr	tgg Trp	ctg Leu 405	gcg Ala	ctt Leu	ctg Leu	acc Thr 410	atc Ile	atg Met	gag Glu	cac His	acc Thr	1249

ctg aat cac ccc tac tga gctgaccctt tgacaccctt cttgtcctcc 1297
 Leu Asn His Pro Tyr *
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 Glu Ala Gln Val Gln Lys Val Lys Glu Leu Glu Asp Leu Glu His Leu
 35 40 45
 Gln Leu Asp Phe Trp Arg Gly Pro Ala His Pro Gly Ser Pro Ile Asp
 50 55 60
 Val Arg Val Pro Phe Pro Ser Ile Gln Ala Val Lys Ile Phe Leu Glu
 65 70 75 80
 Ser His Gly Ile Ser Tyr Glu Thr Met Ile Glu Asp Val Gln Ser Leu
 85 90 95
 Leu Asp Glu Glu Gln Glu Gln Met Phe Ala Phe Arg Ser Arg Ala Arg
 100 105 110
 Ser Thr Asp Thr Phe Asn Tyr Ala Thr Tyr His Thr Leu Glu Glu Ile
 115 120 125
 Tyr Asp Phe Leu Asp Leu Leu Val Ala Glu Asn Pro His Leu Val Ser
 130 135 140
 Lys Ile Gln Ile Gly Asn Thr Tyr Glu Gly Arg Pro Ile Tyr Val Leu
 145 150 155 160
 Lys Phe Ser Thr Gly Gly Ser Lys Arg Pro Ala Ile Trp Ile Asp Thr
 165 170 175
 Gly Ile His Ser Arg Glu Trp Val Thr Gln Ala Ser Gly Val Trp Phe
 180 185 190
 Ala Lys Lys Ile Thr Gln Asp Tyr Gly Gln Asp Ala Ala Phe Thr Ala
 195 200 205
 Ile Leu Asp Thr Leu Asp Ile Phe Leu Glu Ile Val Thr Asn Pro Asp
 210 215 220
 Gly Phe Ala Phe Thr His Ser Thr Asn Arg Met Trp Arg Lys Thr Arg
 225 230 235 240
 Ser His Thr Ala Gly Ser Leu Cys Ile Gly Val Asp Pro Asn Arg Asn
 245 250 255
 Trp Asp Ala Gly Phe Gly Leu Ser Gly Ala Ser Ser Asn Pro Cys Ser
 260 265 270
 Glu Thr Tyr His Gly Lys Phe Ala Asn Ser Glu Val Glu Val Lys Ser
 275 280 285
 Ile Val Asp Phe Val Lys Asp His Gly Asn Ile Lys Ala Phe Ile Ser
 290 295 300
 Ile His Ser Tyr Ser Gln Leu Leu Met Tyr Pro Tyr Gly Tyr Lys Thr
 305 310 315 320
 Glu Pro Val Pro Asp Gln Asp Glu Leu Asp Gln Leu Ser Lys Ala Ala
 325 330 335
 Val Thr Ala Leu Ala Ser Leu Tyr Gly Thr Lys Phe Asn Tyr Gly Ser
 340 345 350
 Ile Ile Lys Ala Ile Tyr Gln Ala Ser Gly Ser Thr Ile Asp Trp Thr
 355 360 365
 Tyr Ser Gln Gly Ile Lys Tyr Ser Phe Thr Phe Glu Leu Arg Asp Thr
 370 375 380
 Gly Arg Tyr Gly Phe Leu Leu Pro Ala Ser Gln Ile Ile Pro Thr Ala
 385 390 395 400
 Lys Glu Thr Trp Leu Ala Leu Leu Thr Ile Met Glu His Thr Leu Asn
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 His Pro Tyr

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<220>
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aag gag gac ttt gtg ggg cat cag gtg ctc cga atc tct gta gcc gat	96
Lys Glu Asp Phe Val Gly His Gln Val Leu Arg Ile Ser Val Ala Asp	
20 25 30	
gag gcc cag gta cag aag gtg aag gag ctg gag gac ctg gag cac ctg	144
Glu Ala Gln Val Gln Lys Val Lys Glu Leu Glu Asp Leu Glu His Leu	
35 40 45	
cag ctg gac ttc tgg cgg ggg cct gcc cac cct ggc tcc ccc atc gac	192
Gln Leu Asp Phe Trp Arg Gly Pro Ala His Pro Gly Ser Pro Ile Asp	
50 55 60	
gtc cga gtg ccc ttc ccc agc atc cag gcg gtc aag atc ttt ctg gag	240
Val Arg Val Pro Phe Pro Ser Ile Gln Ala Val Lys Ile Phe Leu Glu	
65 70 75 80	
tcc cac ggc atc agc tat gag acc atg atc gag gac gtg cag tcg ctg	288
Ser His Gly Ile Ser Tyr Glu Thr Met Ile Glu Asp Val Gln Ser Leu	
85 90 95	
ctg gac gag gag cag gag cag atg ttc gcc ttc cgg tcc cgg gcg cgc	336
Leu Asp Glu Glu Gln Glu Gln Met Phe Ala Phe Arg Ser Arg Ala Arg	
100 105 110	
tcc acc gac act ttt aac tac gcc acc tac cac acc ctg gag gag atc	384
Ser Thr Asp Thr Phe Asn Tyr Ala Thr Tyr His Thr Leu Glu Glu Ile	
115 120 125	
tat gac ttc ctg gac ctg ctg gtg gcg gag aac ccg cac ctt gtc agc	432
Tyr Asp Phe Leu Asp Leu Leu Val Ala Glu Asn Pro His Leu Val Ser	
130 135 140	
aag atc cag att ggc aac acc tat gaa ggg cgt ccc att tat gtg ctg	480
Lys Ile Gln Ile Gly Asn Thr Tyr Glu Gly Arg Pro Ile Tyr Val Leu	
145 150 155 160	
aag ttc agc acg ggg ggc agt aag cgt cca gcc atc tgg atc gac acg	528
Lys Phe Ser Thr Gly Gly Ser Lys Arg Pro Ala Ile Trp Ile Asp Thr	
165 170 175	
ggc atc cat tcc cgg gag tgg gtc acc cag gcc agt ggg gtc tgg ttt	576
Gly Ile His Ser Arg Glu Trp Val Thr Gln Ala Ser Gly Val Trp Phe	
180 185 190	
gca aag aag atc act caa gac tat ggg cag gat gca gct ttc acc gcc	624
Ala Lys Lys Ile Thr Gln Asp Tyr Gly Gln Asp Ala Ala Phe Thr Ala	
195 200 205	
att ctc gac acc ttg gac atc ttc ctg gag atc gtc acc aac cct gat	672
Ile Leu Asp Thr Leu Asp Ile Phe Leu Glu Ile Val Thr Asn Pro Asp	
210 215 220	
ggc ttt gcc ttc acg cac agc acg aat cgc atg tgg cgc aag act cgg	720
Gly Phe Ala Phe Thr His Ser Thr Asn Arg Met Trp Arg Lys Thr Arg	

225	230	235	240	
tcc cac aca gca ggc tcc ctc tgt att ggc gtg gac ccc aac agg aac				768
Ser His Thr Ala Gly Ser Leu Cys Ile Gly Val Asp Pro Asn Arg Asn	245	250	255	
tgg gac gct ggc ttt ggg ttg tcc gga gcc agc agt aac ccc tgc tcg				816
Trp Asp Ala Gly Phe Gly Leu Ser Gly Ala Ser Ser Asn Pro Cys Ser	260	265	270	
gag act tac cac ggc aag ttt gcc aat tcc gaa gtg gag gtc aag tcc				864
Glu Thr Tyr His Gly Lys Phe Ala Asn Ser Glu Val Glu Val Lys Ser	275	280	285	
att gta gac ttt gtg aag gac cat ggg aac atc aag gcc ttc atc tcc				912
Ile Val Asp Phe Val Lys Asp His Gly Asn Ile Lys Ala Phe Ile Ser	290	295	300	
atc cac agc tac tcc cag ctc ctc atg tat ccc tat ggc tac aaa aca				960
Ile His Ser Tyr Ser Gln Leu Leu Met Tyr Pro Tyr Gly Tyr Lys Thr	305	310	315	320
gaa cca gtc cct gac cag gat gag ctg gat cag ctt tcc aag gct gct				1008
Glu Pro Val Pro Asp Gln Asp Glu Leu Asp Gln Leu Ser Lys Ala Ala	325	330	335	
gtg aca gcc ctg gcc tct ctc tac ggg acc aag ttc aac tat ggc agc				1056
Val Thr Ala Leu Ala Ser Leu Tyr Gly Thr Lys Phe Asn Tyr Gly Ser	340	345	350	
atc atc aag gca att tat caa gcc agt gga agc act att gac tgg acc				1104
Ile Ile Lys Ala Ile Tyr Gln Ala Ser Gly Ser Thr Ile Asp Trp Thr	355	360	365	
tac agc cag ggc atc aag tac tcc ttc acc ttc gag ctc cgg gac act				1152
Tyr Ser Gln Gly Ile Lys Tyr Ser Phe Thr Phe Glu Leu Arg Asp Thr	370	375	380	
ggg cgc tat ggc ttc ctg ctg cca gcc tcc cag atc atc ccc aca gcc				1200
Gly Arg Tyr Gly Phe Leu Leu Pro Ala Ser Gln Ile Ile Pro Thr Ala	385	390	395	400
aag gag acg tgg ctg gcg ctt ctg acc atc atg gag cac acc ctg aat				1248
Lys Glu Thr Trp Leu Ala Leu Leu Thr Ile Met Glu His Thr Leu Asn	405	410	415	
cac ccc tac tga				1260
His Pro Tyr *				